IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SEPRACOR INC., Plaintiff, vs. DEY, L.P. and DEY, INC., Defendants.	C.A. No. 06-113-JJF CONSOLIDATED **PUBLIC VERSION**
SEPRACOR INC., Plaintiff, vs. BARR LABORATORIES, INC., Defendant.	

DECLARATION OF IMRON T. ALY IN SUPPORT OF BARR'S OPENING MEMORANDUM REGARDING CLAIM CONSTRUCTION

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Originally filed: April 10, 2008
Public version filed: April 16, 2008

I, IMRON T. ALY, declare and state that:

1. I am a partner at the law firm of Winston & Strawn LLP, located in Chicago, Illinois. I am counsel to Defendant Barr Laboratories, Inc. for this matter.

2. Attached hereto as Exhibit 1 is a true and correct copy of U.S. Patent 5,362,755.

3. Attached hereto as Exhibit 2 is a true and correct copy of U.S. Patent 5,547,994.

4. Attached hereto as Exhibit 3 is a true and correct copy of U.S. Patent 5,760,090.

5. Attached hereto as Exhibit 4 is a true and correct copy of U.S. Patent 5,844,002.

6. Attached hereto as Exhibit 5 is a true and correct copy of U.S. Patent 6,083,993.

7. Attached hereto as Exhibit 6 is a true and correct copy of the following article: Jenny Bryan, *Ventolin Remains a Breath of Fresh Air for Asthma Sufferers, after 40 Years*, 279 The Pharm. J. 404, 404 (October 13, 2007), *available at* http://www.pjonline.com.

8. Attached hereto as Exhibit 7 is a true and correct copy of Sepracor's original Patent Application dated January 5, 1990.

9. Attached hereto as Exhibit 8 is a true and correct copy of the Office Action from the Patent Office dated March 22, 1991.

10. Attached hereto as Exhibit 9 is a true and correct copy of the Office Action from the Patent Office dated December 9, 1991.

11. Attached hereto as Exhibit 10 is a true and correct copy of Sepracor's Amendment sent to the Patent Office dated July 14, 1992.

12. Attached hereto as Exhibit 11 is a true and correct copy of Sepracor's Amendment sent to the Patent Office dated February 10, 1993.

13. Attached hereto as Exhibit 12 is a true and correct copy of the Gunnar Aberg Declaration sent to the Patent Office February 10, 1993.

14. Attached hereto as Exhibit 13 is a true and correct copy of Sepracor's Amendment sent to the Patent Office dated July 23, 1993.

15. Attached hereto as Exhibit 14 is a true and correct copy of Sepracor's Preliminary Remarks sent to the Patent Office dated December 7, 1993.

16. Attached hereto as Exhibit 15 is a true and correct copy of Sepracor's Amendment sent to the Patent Office dated June 9, 1995.

17. Attached hereto as Exhibit 16 is a true and correct copy of Sepracor's Interview Summary sent to the Patent Office dated January 24, 1996.

18. Attached hereto as Exhibit 17 is a true and correct copy of Sepracor's Amendment sent to the Patent Office dated May 7, 1997.

19. Attached hereto as Exhibit 18 is a true and correct copy of Sepracor's Amendment sent to the Patent Office dated November 20, 1997.

20. Attached hereto as Exhibit 19 is a true and correct copy of Sepracor's Amendment sent to the Patent Office dated April 21, 1998.

21. Attached hereto as Exhibit 20 is a true and correct copy of Sepracor's Amendment sent to the Patent Office dated December 17, 1999.

22. Attached hereto as Exhibit 21 is a true and correct copy of an excerpt from the transcript of the deposition of Dr. James Young, named co-inventor on the asserted patents, dated August 15, 2007. The deposition was marked Confidential by Sepracor.

I declare under penalty of perjury under the laws of the state of Illinois that the foregoing is true and correct to the best of my knowledge and that this declaration was executed on this 10th day of April, 2008 at Chicago, Illinois.

By: _____
IMRON T. ALY

EXHIBITS IN SUPPORT OF
BARR'S OPENING MEMORANDUM
REGARDING CLAIM CONSTRUCTION

U.S. Patent 5,362,755 .....Exhibit 1

U.S. Patent 5,547,994 .....Exhibit 2

U.S. Patent 5,760,090 .....Exhibit 3

U.S. Patent 5,844,002 .....Exhibit 4

U.S. Patent 6,083,993 .....Exhibit 5

Ventolin Remains a Breath of Fresh Air for Asthma Sufferers, after 40 Years .....Exhibit 6

Sepracor's 1/5/90 Application .....Exhibit 7

3/22/91 Office Action .....Exhibit 8

12/9/91 Office Action .....Exhibit 9

Sepracor's 7/14/92 Amendment .....Exhibit 10

Sepracor's 2/10/93 Amendment .....Exhibit 11

2/10/93 Aberg Declaration.....Exhibit 12

Sepracor's 7/23/93 Amendment .....Exhibit 13

Sepracor's 12/7/93 Preliminary Remarks .....Exhibit 14

Sepracor's 6/9/95 Amendment .....Exhibit 15

Sepracor's 1/24/96 Interview Summary .....Exhibit 16

Sepracor's 5/7/97 Amendment .....Exhibit 17

Sepracor's 11/20/97 Amendment .....Exhibit 18

Sepracor's 4/21/98 Amendment .....Exhibit 19

Sepracor's 12/17/99 Amendment .....Exhibit 20

Excerpt from Transcript of 8/15/07 Young Deposition.....Exhibit 21

EXHIBIT 1

US005362755A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,362,755

[45] Date of Patent: Nov. 8, 1994

[54] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[21] Appl. No.: 163,581

[22] Filed: Dec. 7, 1993

Related U.S. Application Data

[63] Continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[5] A61K 31/135

[52] U.S. Cl. 514/649; 514/826

[58] Field of Search 514/649, 826

[56] References Cited

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2255503 7/1992 United Kingdom .

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Primary Examiner—Raymond J. Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg

[57] ABSTRACT

The optically pure R(−) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(−) isomer of albuterol for treating asthma while minimizing the side effects associated with chronic administration of racemic albuterol.

7 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

This application is a continuation of application Ser. No. 07/896,725 filed Jun. 9, 1992 now abandoned which is a continuation of copending application Ser. No. 07/461,262 filed on Jan. 5, 1990 now abandoned.

DESCRIPTION

1. Background

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broncho-dilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(-tert-butylamino) methyl]-4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the

optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim 1 wherein the amount of the R(−) isomer of albuterol is greater than approximately 90% by weight of total albuterol.

3. A method of claim 2 wherein the amount of the R(−) isomer of albuterol is greater than 99% by weight of total albuterol.

4. A method of claim 1 comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(−) isomer of albuterol per dose.

5. A method of claim 1 comprising orally administering to the individual from approximately 1 mg to approximately 8 mg of the R(−) isomer of albuterol two to four times daily.

6. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration or racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

7. A method of claim 6 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

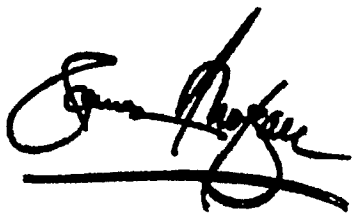
PATENT NO. : 5,362,755
DATED : November 8, 1994
INVENTOR(S) : Barbarich et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4,
Line 30, delete the word "or" and insert the word -- of --

Signed and Sealed this

Thirtieth Day of September, 2003



JAMES E. ROGAN
Director of the United States Patent and Trademark Office

EXHIBIT 2

US005547994A

United States Patent [19]

Barberich et al.

[11] **Patent Number: 5,547,994**

[45] **Date of Patent: Aug. 20, 1996**

[54] **METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(–) ALBUTEROL**

[75] Inventors: **Timothy J. Barberich**, Concord; **James W. Young**, Still River, both of Mass.

[73] Assignee: **Sepracor, Inc.**, Marlborough, Mass.

[21] Appl. No.: **335,480**

[22] Filed: **Nov. 7, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] **Int. Cl.**[6] **A61K 31/135**

[52] **U.S. Cl.** **514/649**; 514/826

[58] **Field of Search** 514/649, 826

[56] **References Cited**

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5,362,755 11/1994 Barberich et al. 514/649

FOREIGN PATENT DOCUMENTS

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Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] **ABSTRACT**

The optically pure R(–) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(–) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

6 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(−) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993 and now U.S. Pat. No. 5,362,755, which was a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992, now abandoned, which was a continuation of application Ser. No. 07/461,262 filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1 [(tert-butylamino) methyl] -4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a par-

ticular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(–) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(–) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(–) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim **1** wherein the amount of the R(–) isomer of albuterol is greater than approximately 90% by weight.

3. A method of claim **2** wherein the amount of the R(–) isomer of albuterol is greater than 99% by weight.

4. A method of claim **1** comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(–) isomer of albuterol per dose.

5. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(–) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

6. A method of claim **5** wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

* * * * *

EXHIBIT 3

US005760090A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,760,090

[45] Date of Patent: *Jun. 2, 1998

[54] **METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(−) ALBUTEROL**

[75] Inventors: **Timothy J. Barberich**, Concord; **James W. Young**, Still River, both of Mass.

[73] Assignee: **Sepracor, Inc.**, Marlborough, Mass.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,362,755.

[21] Appl. No.: **691,604**

[22] Filed: **Aug. 15, 1996**

Related U.S. Application Data

[63] Continuation of Ser. No. 335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] **Int. Cl.**[6] **A61K 31/135**

[52] **U.S. Cl.** **514/649**; 514/826

[58] **Field of Search** 514/649

[56] **References Cited**

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Chapman et al. "Racemic mixtures at root of worsening symptom? Active enantiomers . . . " *TIPS* 13, 231–232 (1992).

Muittari et al. "Comparison of acute bronchodilator effects of oral salbutamol. . . . " *Chem. Abstr.* 89: 123259m (1978).

Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] **ABSTRACT**

The optically pure R(−) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(−) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

9 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(−) ALBUTEROL

This is a continuation of U.S. application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which is a continuation of U.S. application Ser. No. 08/163,581 filed Dec. 7, 1993, now U.S. Pat. No. 5,362,755, which is a continuation of U.S. application Ser. No. 07/896,725, filed Jun. 9, 1992, abandoned, which is a continuation of U.S. application Ser. No. 07/461,262, filed Jan. 5, 1990, abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broncho-dilation activity of the R(−) enantiomer of albuterol to provide relief from

bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(tert-butylamino) methyl]-4-hydroxy-m-xylene-α, α-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or

propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating asthma, while reducing side effects associated with the administration of racemic albuterol, comprising administering to an individual suffering from asthma a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method according to claim **1**, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim **1**, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim **1**, wherein the optically pure R(−) albuterol is administered by inhalation.

5. A method according to claim **4**, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim **1**, wherein the optically pure R(−) albuterol is administered orally.

7. A method according to claim **6**, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim **6**, wherein the optically pure R(−) albuterol is administered as a syrup.

9. A method according to claim **7**, wherein the optically pure R(−) albuterol is administered as a syrup.

* * * * *

EXHIBIT 4

US005844002A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,844,002

[45] Date of Patent: Dec. 1, 1998

[54] **METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(–) ALBUTEROL**

[75] Inventors: **Timothy J. Barberich**, Concord; **James W. Young**, Still River, both of Mass.

[73] Assignee: **Sepracor, Inc.**, Marlborough, Mass.

[21] Appl. No.: **63,551**

[22] Filed: **Apr. 21, 1998**

Related U.S. Application Data

[63] Continuation of Ser. No. 691,604, Aug. 15, 1996, Pat. No. 5,760,090, which is a continuation of Ser. No. 335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] **Int. Cl.**[6] **A61K 31/135**

[52] **U.S. Cl.** **514/649**; 514/826

[58] **Field of Search** 514/649, 826

[56] **References Cited**

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Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] **ABSTRACT**

The optically pure R(–) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(–) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

10 Claims, No Drawings

METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(−) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 08/691,604, filed Aug. 15, 1996, now U.S. Pat. No. 5,760,090, which is a continuation of application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which is a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993 now U.S. Pat. No. 5,362,755, which is a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992 now abandoned, which was a continuation of application Ser. No. 07/461,262, filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broncho-dilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(tert-butylamino) methyl] -4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more)

drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of inducing bronchodilation or providing relief of bronchospasm, comprising administering to an individual a quantity of optically pure R-(−) albuterol sufficient to induce said bronchodilation.

2. A method according to claim **1**, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim **1**, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim **1**, wherein the optically pure R(−) albuterol is administered by inhalation.

5. A method according to claim **4**, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim **1**, wherein the optically pure R(−) albuterol is administered orally.

7. A method according to claim **6**, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim **6**, wherein the optically pure R(−) albuterol is administered as a syrup.

9. A method according to claim **7**, wherein the optically pure R(−) albuterol is administered as a syrup.

10. A method of inducing bronchodilation or providing relief of bronchospasm while reducing the concomitant liability of adverse effects associated with racemic albuterol, comprising administering to an individual a quantity of optically pure R-(−) albuterol sufficient to induce said bronchodilation while simultaneously reducing said adverse effects.

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EXHIBIT 5

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United States Patent [19]

Barberich et al.

[11] Patent Number: 6,083,993

[45] Date of Patent: *Jul. 4, 2000

[54] METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R(−) ALBUTEROL

[75] Inventors: **Timothy J. Barberich**, Concord; **James W. Young**, Still River, both of Mass.

[73] Assignee: **Sepracor Inc.**, Marlborough, Mass.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **09/466,107**

[22] Filed: **Dec. 17, 1999**

Related U.S. Application Data

[63] Continuation of application No. 09/200,541, Nov. 25, 1998, which is a continuation of application No. 09/063,551, Apr. 21, 1998, Pat. No. 5,844,002, which is a continuation of application No. 08/691,604, Aug. 15, 1996, Pat. No. 5,760,090, which is a continuation of application No. 08/335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of application No. 08/163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of application No. 07/896,725, Jun. 9, 1992, abandoned, which is a continuation of application No. 07/461,262, Jan. 5, 1990, abandoned.

[51] **Int. Cl.**[7] **A61K 31/135**

[52] **U.S. Cl.** **514/649**

[58] **Field of Search** 514/649

[56] **References Cited**

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Muittari et al. "Comparison of acute bronchodilator effects of oral salbutamol, . . . " *Chem. Abstr. 89*: 123259m (1978).

Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] **ABSTRACT**

The optically pure R(–) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(–) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

17 Claims, No Drawings

METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R(−) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of our prior copending application Ser. No. 09/200,541, filed Nov. 25, 1998, which is a continuation of application Ser. No. 09/063,551, filed Apr. 21, 1998, now U.S. Pat. No. 5,844,002, which was a continuation of application Ser. No. 08/691,604, filed Aug. 15, 1996, now U.S. Pat. No. 5,760,090, which was a continuation of application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which was a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993, now U.S. Pat. No. 5,362,755, which was a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992 now abandoned, which was a continuation of application Ser. No. 07/461,262, filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may nave an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs.

In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(tert-butylamino) methyl]-4-hydroxy-mxylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine

or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

What is claimed is:

1. A method of treating bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(−) albuterol.

2. A method according to claim **1**, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim **1**, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim **1**, wherein the optically pure R(−) albuterol is administered by inhalation.

5. A method according to claim **4**, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim **1**, wherein the optically pure R(−) albuterol is administered orally.

7. A method according to claim **6**, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim **6**, wherein the optically pure R(−) albuterol is administered as a tablet, capsule or syrup.

9. A method according to claim **7**, wherein the optically pure R(−) albuterol is administered as a syrup.

10. A method of preventing bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(−) albuterol.

11. A method according to claim **10**, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

12. A method according to claim **10**, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

13. A method according to claim **10**, wherein the optically pure R(−) albuterol is administered by inhalation.

14. A method according to claim **13**, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

15. A method according to claim **10**, wherein the optically pure R(−) albuterol is administered orally.

16. A method according to claim **15**, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

17. A method according to claim **15**, wherein the optically pure R(−) albuterol is administered as a tablet, capsule or syrup.

* * * * *

EXHIBIT 6

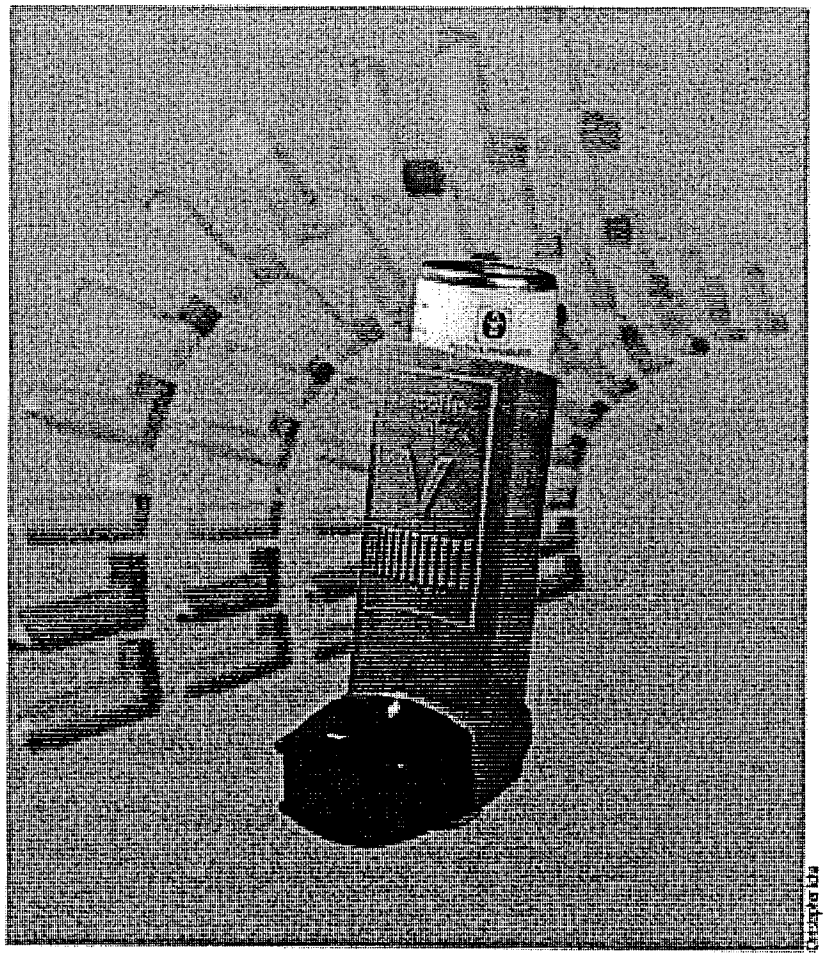
Ventolin remains a breath of fresh air for asthma sufferers, after 40 years

In the first article in a series on landmark drugs, **Jenny Bryan** retells the history of Ventolin and explains why it still plays a major role in the treatment of asthma

When Allen & Hanburys launched the first selective β_2-receptor agonist, Ventolin (salbutamol), in 1968, the drug was an instant success. With asthma mortality peaking at over 2,000 deaths per year in the mid 1960s, an effective bronchodilator that specifically targeted the β_2-receptors of the lungs was immediately seen as an important advance.

"There was precious little before Ventolin for routine bronchodilation," recalls Tim Clark, professor of pulmonary medicine at the National Heart and Lung Institute, Imperial College, London. "We used isoprenaline, but its lack of selectivity for bronchial smooth muscle meant that it caused tachycardia and there was concern that it could be linked with the asthma deaths.

"The only other drugs we had to treat asthma symptoms were adrenaline and aminophylline for severe asthma, and theophylline and ephedrine for chronic asthma. Other preparations for chronic asthma included sedatives such as barbiturates," he explains. "So there were great expectations for Ventolin because it was a good bronchodilator, it lasted longer than isoprenaline and it didn't have the cardiac side effects. It was hoped that Ventolin would be of great use for both acute and chronic asthma."



Development of salbutamol

The development of salbutamol followed the discovery in the early 1960s that beta adrenoceptors had two subtypes — β_1 found predominantly in the heart and β_2 in smooth muscle such as that in the lungs.[1] Allen & Hanburys chemists therefore set to work to make analogues of isoprenaline which were more specific to the β_2-receptor. They were rewarded with salbutamol, which was over 500 times more potent at the β_2- than the β_1-receptor.[2]

Activation of the β_2-receptor is understood to relax the airways by increasing intracellular cyclic adenosine monosphosphate (cAMP), which leads to phosphorylation of regulatory proteins that control muscle tone, reduction in the release of intracellular calcium and reduced sensitivity of contractile proteins.[3] The β_2-receptor straddles the cell membrane in a series of seven loops and becomes activated when it is coupled with the Gs protein and guanine triphosphate. It is thought that β_2-agonists work by stabilising β_2-receptors in their activated form, so that the bronchial smooth muscle is relaxed and the airways dilated.[3]

Ventolin lived up to expectations and it was not long before it had almost replaced isoprenaline and become the mainstay of asthma treatment with a liquid formulation suitable for nebulisation, as well as oral preparations added to the range. Other short acting β_2-agonists followed, such as Astra's terbutaline (Bricanyl) and Boehringer Ingelheim's fenoterol (Berotec). But Ventolin cornered the market; not only was it first, it was British.

Race for a long-acting β_2-agonist

The new race was to develop a long-acting β_2-agonist which would be as selective and free of cardiac side effects as salbutamol and provide symptom relief well beyond the four hours achieved with the first generation, short-acting drugs. At Allen & Hanburys, the aim was to find a way to anchor a selective β_2-agonist to its receptor for prolonged periods, thus extending its activity. The solution proved to be salmeterol (Serevent) — the first long-acting β_2-agonist (LABA). Launched in 1990, it was subsequently shown to achieve its 12-hour duration of action by binding to the β_2-receptor at the active site and at a second "exosite" on the receptor at a point close to the junction of the cell membrane and the cytoplasm.[4]

But, just as Ventolin had been launched against a backdrop of rising asthma mortality in the mid 1960s, salmeterol and its rival formoterol (Oxis) made by Astra, came onto the market with asthma deaths on the rise.

Increase in death of asthma patients

During the 1980s, an increase in asthma deaths in New Zealand was linked to the over use of fenoterol, a short-acting β-agonist marketed in a high-dose preparation with β_1-agonist activity comparable to that of isoprenaline and with similar accompanying cardiac side effects.[5] The rise in asthma deaths in New Zealand started in 1976, the year of fenoterol's highly successful introduction. In response to epidemiological evidence of a link between fenoterol and asthma deaths, three case-control studies were carried out, all showing a link between fenoterol use and asthma deaths.[5] The product was removed from the New Zealand drug tariff in 1989 and then withdrawn from the market. Asthma deaths subsequently fell back to pre-fenoterol levels. British rates never reached those seen in New Zealand and fenoterol was not widely used in the UK, but mortality did rise again through the late 1980s to peak once more at nearly 2,000 deaths per year. Although the rise occurred before the introduction of salmeterol, there were concerns that LABAs could exacerbate the problem and the finger of suspicion was soon pointing in their direction.

"The problem will always be that severe asthma is associated with deaths and the more severe a person's asthma, the more they use their bronchodilator, so it's always going to be difficult to unravel the link," explains Professor Clark. "I used to liken it to finding a person dead in the desert grasping an empty water bottle. Would you assume that it was the water which had killed him?"

A recent contributor to the controversy — the Salmeterol Multicenter Asthma Research Trial (SMART) — showed small, statistically significant increases in respiratory-related and asthma-related deaths and combined asthma-related deaths or life-threatening experiences in asthma patients who took salmeterol in addition to their usual treatment, compared with placebo.[6] Subgroup analyses suggested that the risk was greater in African Americans compared with Caucasian subjects and in those not taking inhaled corticosteroids.

Both UK and US guidance now stress the importance of only using LABAs in combination with inhaled steroids. But, with mortality rates in the UK back down to about 1,300 in 2005, it may be time for a short pause in the long-running debate.

Whatever the eventual conclusions, Ventolin has remained free of the claims and counter-claims which have left question-marks over the LABAs. Indeed, as Professor Clark points out, it is now used not only to relieve the symptoms of asthma, but as a measure of asthma control. Patients who need more than a few puffs per week of their Ventolin do not have full control of their asthma and probably need to step up their other treatment.

"Ventolin has undoubtedly stood the test of time for relief of symptoms and measuring asthma control and, although most people are now prescribed generic salbutamol, people still call it Ventolin and a surprising number do still get the original brand," Professor Clark said.

After nearly 40 years and many millions of blue puffers since its launch, the name Ventolin has become to asthma what Hoover is to housework.

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EXHIBIT 7

PATENT APPLICATION
Docket No.: SPC89-05

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January 5, 1990

The Honorable Commissioner
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Sir:

Transmitted herewith for filing is the patent application of

Inventor(s): Timothy J. Barberich and James W. Young

For: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

- [X] Specification, Claims, Abstract of the Disclosure
- [ ] 0 sheets of formal/informal drawings.
- [ ] An assignment of the invention to _____
- [ ] A verified statement to establish small entity status under 37 C.F.R. 1.9 and 37 C.F.R. 1.27.
- [X] ~~Executed~~/Unexecuted Combined Declaration/Power of Attorney.
- [ ] Other: _____

The filing fee has been calculated as shown below:

	(Col. 1)	(Col. 2)	SMALL ENTITY		OTHER THAN A SMALL ENTITY	
FOR	NO. FILED	NO. EXTRA	RATE	FEE	RATE	FEE
BASIC FEE				$185		$370
TOTAL CLAIMS	12 - 20 =	0	x 6 =	$	x 12 =	$ 0
INDEP CLAIMS	3 - 3 =	0	x18 =	$	x 36 =	$ 0
☐ MULTIPLE DEPENDENT CLAIM PRESENTED			+60 =	$	+120 =	$
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			TOTAL:	$	TOTAL:	$ 370

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- ☒ Any filing fees under 37 C.F.R. 1.16 for presentation of extra claims.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

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Dated: January 5, 1990

SPC89-05
1/4/90

PATENT APPLICATION
DOCKET NO: SPC89-05

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

Description

Background

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a

specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

Summary of the Invention

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(-) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broncho-dilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(-) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is

administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

Detailed Description of the Invention

The present invention relies on the bronchodilation activity of the R(-) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(-) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(-) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(tert-butylamino) methyl]-4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(-) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily

obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(-) isomer of albuterol is administered to an individual who has asthma. For example, R(-) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(-) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(-) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(-) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of

administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(-) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(-) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(-) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in

tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(-) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(-) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine

experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

1. A method of treating asthma in an individual with albuterol, while reducing side effects associated with albuterol, comprising administering to the individual a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation, said R isomer being substantially free of its S(+) isomer.

2. A method of Claim 1 wherein the amount of the R(-) isomer of albuterol is greater than approximately 90% by weight of total albuterol

3. A method of Claim 2 wherein the amount of the R(-) isomer of albuterol is greater than 99% by weight of total albuterol

4. A method of Claim 1 comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(-) isomer of albuterol per dose.

5. A method of Claim 1 comprising orally administering to the individual from approximately 1 mg to approximately 8 mg of the R(-) isomer of albuterol two to four times daily.

6. A method of treating asthma in an individual with albuterol, while reducing side effects associated with albuterol, comprising administering to the individual a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation and at least one additional drug.

7. A method of Claim 6 wherein the additional drug is selected from the group consisting of: bronchodilators, antihistamines and analgesics.

8. A method of Claim 7 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

9. A composition comprising an optically pure R(-) isomer of albuterol and at least one additional drug.

10. A composition of Claim 9 containing at least 90% by weight of the R(-) isomer of albuterol.

11. A composition of Claim 10 containing at least 99% by weight of the R(-) isomer of albuterol.

12. A composition of Claim 9 wherein the additional drug is selected from the group consisting of: bronchodilators, antihistamines and analgesics.

08/163581

METHOD FOR TREATING ASTHMA USING
OPTICALLY PURE R(-) ALBUTEROL

Abstract of the Disclosure

The optically pure R(-) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptons associated with asthma in individuals. A method is disclosed utilizing the optically pure R(-) isomer of albuterol for treating asthma while minimizing the side effects associated with chronic administration of racemic albuterol.

EXHIBIT 8

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY
07/461,262	01/05/90	BARBERICH	T 8PC8905

EXAMINER
SCHENKMAN, L

ART UNIT | PAPER
125 | 9

DATE MAILED: 03/22/91

HAMILTON, BROOK, SMITH & REYNOLDS
TWO MILITIA DRIVE
LEXINGTON, MA 02173-4799

There is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on 12-24-90 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-11 and 12 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-11 and 12 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-12 are rejected under 35 U.S.C. § 103 as being unpatentable over Chemical Abstracts for reasons of record. Applicants arguments regarding unpredictability are not persuasive in view of the cited decision.

Claims 1-5 are rejected under 35 U.S.C. § 103 as being unpatentable over Brittain et al, Hartley et al, Hawkins et al and Buckner et al who teach compositions containing the claimed compounds (e.g water or saline solution) and its isomers used as a bronchodilator in the treatment of asthma. The references further teach greater bronchodilation activity of the R (-) isomer over the S(+) isomer. The use therefor, of compositions containing mainly the R (-) isomer in the treatment of asthma is clearly rendered obvious by the prior art.

Claims 6-12 are rejected under 35 U.S.C. § 103 as being unpatentable over the references supra in further view of Chemical Abstracts which shows combination of drugs, including salbutomal, used in the treatment of asthma.

Claims 6 and 9-11 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. No basis for the mixture of isomers set forth in claims 10 and 11 can be found in claim 9 which is limited to a single isomer. Claim 9 is incorrect is not including the R(-) isomer. Compare with original claim 9. Claims 9-12 are again deemed to be too broad absent proportions of ingredients. The term "additional drug" (claims 6 and 9-11) is too broad.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. Schenkman whose telephone number is (703) 308-0091.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Leonard Schenkman

SCHENKMAN:drb
March 13, 1991

LEONARD SCHENKMAN
EXAMINER
ART UNIT 125

FORM PTO-1449 (MOD. 1989) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTY. DOCKET NO. SPC89-05

SERIAL NO. 07/463,581

APPLICANT Timothy J. Barberich, et al.

FILING DATE January 5, 1990

GROUP 125

LIST OF ART CITED BY APPLICANT

(Use several sheets if necessary)

RECEIVED 91 JAN -8 PM 1:20 GROUP 220

Sheet 1 of 2

MAIL ROOM DEC 21 1990 PATENT & TRADEMARK OFFICE

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIA
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						
	AJ						
	AK						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AL							
	AM							
	AN							
	AO							
	AP							

OTHER ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	AR	R.T. Brittain et al., Br. J. Pharmacol., 48:144-147 (1973)
	AS	C.J. Hawkins and G.T. Klease, J. Med. Chemistry, 16(7):856-857 (1973)
	AT	D. Hartley and D. Middlemiss, J. Med. Chemistry, 14(9):895 (1971)

EXAMINER L. Hollenbeck

DATE CONSIDERED 1-14-91

Sheet 2 of 2

ATTY. DOCKET NO.	SERIAL NO.
SPC89-05	07/461,262
APPLICANT: Timothy J. Barberich, et al.	
FILING DATE: January 5, 1990	GROUP: 125

U.S. PATENT DOCUMENTS

EXAMINER	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

MAIL ROOM DEC 28 1990 PAT. & TRADEMARK OFF.

RECEIVED 91 JAN -8 AM 10:56 GROUP 120

OTHER ART (Including Author, Title, Date, Pertinent Pages, Etc.)

AU	C.K. Buckner and P. Abel, J. Pharmacol. Exp. Ther., 189(3):616-625 (1974)

Examiner: [signature] Date Considered: 3-11-91

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

EXHIBIT 9

UT.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

ADDRESS: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/461,262	01/05/90	BARBERICH T	SPC8905

EXAMINER
SCHENKMAN, L

HAMILTON, BROOK, SMITH & REYNOLDS
TWO MILTIA DRIVE
LEXINGTON, MA 02173-4799

ART UNIT	PAPER NUMBER
1205	13

DATE MAILED: 12/09/91

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on 9/26/91 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION:

1. ☒ Claims 1-6, 8, 9, 13 and 14 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-6, 8, 9, 13 and 14 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☒ Other

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-6, 8, 9, 13 and 14 are rejected under 35 U.S.C. § 103 as being unpatentable over Chemical Abstracts for reasons of record. Applicant's arguments and analysis of the In re Adamson decision are not well taken. The fact that Adamson does not relate to treatment of asthma or use of the claimed isomer is not germane since the claimed isomer has the same type of activity as the racemic mixture.

Claims 1-5 are rejected under 35 U.S.C. § 103 as being unpatentable over Brittain et al., Hartley et al., Hawkins et al. and Buckner et al. for reasons of record. Applicant's argument that the prior art teaches that the (-) isomer and the racemic mixture exhibit the same degree of activity is not universally accepted; note that Hawkins et al. article. In any event, since

it has been established that the racemic mixture and isomeric forms of the compounds have been used or tested as bronchodilators in the treatment of asthma, the use of compositions containing the claimed isomer in the treatment of asthma is clearly rendered obvious, notwithstanding the inconsistancy or the prior art on the this point. The references cited herein would present a strong prima facia case of obviousness even assuming, arguendo, they dealt solely with the racemic mixture.

Claims 6, 8, 9, 13 and 14 are rejected under 35 U.S.C. § 103 as being unpatentable over Brittain et al. Hartley et al. Hawkins et al. and Bruckner et al. in view of Chemical Abstracts for reasons of record. The fact that Chemical Abstracts does not teach the isomers of Albuterol is not germane to this rejection. Drug combinations containing the (-) isomer would clearly be obvious in view of the teaching of drug combinations containing the racemic mixture.

Claims 9, 13 and 14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13 and 14 do not have proper antecedent support in claim 9 which appears to be limited to the (-) isomer. Claims 9, 13 and 14 are again rejected as being too broad absent recitation of amounts of ingredients present. The

skilled artisan would be hard pressed to determine contemplated proportions; note the functional language of claim 6.

Tan et al. is cited to show the state of the art.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Schenkman whose telephone number is (703) 308-4651.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

LEONARD SCHENKMAN
EXAMINER
ART UNIT 1205

Schenkman: ach
December 05, 1991

Sheet 1 of 1

MAIL ROOM SEP 27 1991 PAT. & TRADEMARK

ATTY. DOCKET NO. SPC89-05

SERIAL NO. 07/463,587 ~~07/461,262~~

APPLICANT Timothy J. Barberich and James W. Young

FILING DATE January 5, 1990

GROUP 125

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

OTHER ART (Including Author, Title, Date, Pertinent Pages, Etc.)

AV		Tan et al., "Analysis of Salbutomol Enantiomers in Human Urine by Chiral High Performance Liquid Chromatography and Preliminary Studies Related to the Stereoselective Disposition Kinetics in Man", J. Chromatogr., 422, 187-95 (1987)

Examiner [signature] Date Considered 11-1991

EXHIBIT 10

SPC89-05'Pre A
RWW12
7/14/92
RWW/bjn

PATENT APPLICATION
Docket No. SPC89-05

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Timothy J. Barberich and James W. Young

Serial No.: 07/896,725 Group Art Unit: 1205

Filed: June 9, 1992 Examiner: L. Schenkman

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231 on 7-14-92

Hamilton, Brook, Smith & Reynolds, P.C.

B.J. Kenna 7-14-92
Signature Date

PRELIMINARY AMENDMENT

The Honorable Commissioner
of Patents and Trademarks
Washington, D. C. 20231

Sir:

Please amend the above-identified Application as follows:

In the Claims:

In Claim 1, line 6, between "bronchodilation" and the "," insert --while simultaneously reducing undesirable side effects---;

In Claim 6, line 6, between "bronchodilation" and "and" insert ---while simultaneously reducing undesirable side effects---;

In Claim 9, line 2, delete "an optically pure" and instead insert ---the---.

REMARKS

The instant Application is a contination of Application Serial No. 07/461,262 ("the parent case").

The above amendments to the Claims have been made to more distinctly claim the subject matter of the invention. Support for these amendments can be found on page 2, line 6-page 3, line 6; page 3, lines 8-14; and page 6, lines 14-27 of the specification. The relationship between these amendments to the Claims and the response to the Office Action of December 9, 1991 in the parent case will be more fully explained below.

Rejection of Claims 1-6, 8, 9, 13 and 14 under 35 U.S.C. §103.

Claims 1-6, 8, 9, 13 and 14 were rejected under 35 U.S.C. §103 over Chemical Abstracts which, as previously stated by the Examiner, teaches salbutamol (albuterol) used to treat asthma and compositions containing albuterol. The case, In re Adamson et al., was cited as teaching that the difference in activity between isomers is not unexpected.

Applicants respectfully submit that the claims, as amended, overcome the rejection. The Chemical Abstracts reference shows the bronchodilation effects of salbutamol and drug combinations incorporating salbutamol. However, this reference does not teach the use of a quantity of the R(-) isomer of albuterol sufficient to cause bronchodilation while simultaneously reducing undesirable side effects associated with racemic albuterol.

Although In re Adamson et al. teaches that optical isomers themselves are unpatentable over compounds that the art recognizes as having optical isomers, it is not correct to assume from this that a new method for using an isomer is unpatentable, particularly where, as here, the method unexpectedly provides therapeutic effects without causing undesirable side effects.

One would be led to assume, from the Examiner's apparent interpretation of In re Adamson et al., that the physiological effects of a racemic compound, both therapeutic and adverse, are elicited by the same isomer. However, this assumption is contrary to Applicants' disclosure which teaches that undesirable side effects are associated with the racemic mixture or the therapeutically inactive isomer, i.e. the S(+) isomer, of albuterol, but not with the R(-) isomer. Applicants have, therefore, made the unexpected disclosure that the claimed isomer does not have the same type of activity as the racemic mixture.

Rejection of Claims 1-5 under 35 U.S.C. §103.

Claims 1-5 have been rejected under 35 U.S.C. §103 as being unpatentable over Brittain et al., Hartley et al., Hawkins et al., and Buckner et al. who, as previously stated by the Examiner, teach compositions containing the claimed compounds with its isomers used as a bronchodilator in the treatment of asthma and, further, that the R(-) isomer has greater bronchodilation activity over the S(+) isomer.

Applicants respectfully submit that the Claims, as amended, also overcome this rejection. In addition to a complete lack of agreement among the cited references concerning the relative efficacies of the R(-) isomer and the racemate, there is no teaching in these references regarding the administration of a quantity of the R(-) isomer sufficient to effect bronchodilation but without

causing undesirable side effects. The references do not indicate that undesirable side effects can be minimized by administering one of the isomers. Only Applicants' disclosure reveals and claims this important method by administering the R(-) isomer of albuterol.

Rejection of Claims 6, 8, 9, 13 and 14 under 35 U.S.C. §103.

Claims 6, 8, 9, 13 and 14 have been rejected under 35 U.S.C. §103 as being unpatentable over Brittain et al., Hartley et al.; Hawkins et al. and Buckner et al. in view of Chemical Abstracts which, as previously stated by the Examiner, shows combinations of drugs, including salbutamol, used in the treatment of asthma.

Applicants respectfully traverse this rejection, particularly as applied to the presently amended Claims. Although drug combinations including racemic salbutamol are shown in Chemical Abstracts, there is no indication that a combination containing the R(-) isomer minimizes the undesirable side effects associated with the racemic mixture of albuterol. The combination of the other cited references also does not show this element. The combination of drugs which includes the R(-) isomer would not be obvious since undesirable side effects would be expected to be associated with it; there would be no benefit associated with using the R(-) isomer compared with using the racemic mixture. However, Applicants' disclosure shows that undesirable side effects are minimized when the R(-) isomers used. Thus, the combination of drugs including R(-) albuterol is not an obvious extension of a combination of drugs including racemic albuterol.

Rejection of Claims 9, 13 and 14 under 35 U.S.C. §112, second paragraph.

Claims 9, 13 and 14 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. It was stated that Claims 13 and 14 do not have proper antecedent support in Claim 9. Claims 9, 13 and 14 were also rejected as being too broad absent recitation of amounts of ingredients present.

Claim 9 has been presently amended to remove the phrase "optically pure". It is believed that Claims 13 and 14 now have proper antecedent basis and specify the amount of purity of the R(-) isomer of albuterol.

Applicants again respectfully traverse the rejection of Claims 9, 13 and 14 because recitations of amounts of ingredients are dependent on a number of physiological factors which make specification of quantities uncertain until the physiological features are known. It is submitted that skilled artisans, when these features are known, can determine the amounts of ingredients based on these physiological factors.

CONCLUSIONS

With the above amendments and for the above stated reasons, Applicants believe the 35 U.S.C. §§103 and 112, second paragraph rejections have been overcome. Applicants respectfully request reconsideration of the Application and allowance thereof.

If the Examiner feels that a telephone conversation would expedite the prosecution of this Application, he is asked to call Applicant's Agent at (617) 861-6240.

Respectfully submitted,

Richard W. Wagner

Richard W. Wagner
Registration No. 34,480
Agent for Applicant

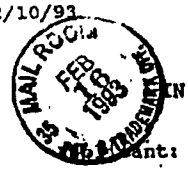
Lexington, MA 02173
Dated: July 14, 1992

EXHIBIT 11

SPC89-05'
RWW13
2/10/93

PATENT APPLICATION
Docket No. SPC89-05'

#23/L
JRP
3/18/93



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Timothy J. Barberich and James W. Young

Serial No.: 07/896,725 Group Art Unit: 1205

Filed: June 9, 1992 Examiner: L. Schenkman

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231 on 2/10/93

Hamilton, Brook, Smith & Reynolds, P.C.

B. J. Hennis 2/10/93
Signature Date

AMENDMENT C

The Honorable Commissioner
of Patents and Trademarks

Washington, D.C. 20231

Dear Sir:

This is in response to the official action of August 10, 1992, which in view of the petition for a three month extension of time submitted herewith, requires response by February 10, 1993.

Please amend the application as follows:

In the Claims:

Please cancel claims 9, 13 and 14 and substitute therefor new claims 15, 16, 17 and 18.

15. A pharmaceutical composition comprising:
    (a) a first component consisting of an antiasthmatically effective amount of albuterol, said albuterol consisting of about 90 to 100% by weight of its R(-) isomer; and
    (b) a second component consisting of a physiologically effective amount of a drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

16. A composition according to claim 15 wherein said second component is an antiasthmatically effective amount of theophylline or terbutaline.

17. A composition according to claim 15 wherein said second component is an analgesically effective amount of a drug selected from the group consisting of aspirin, acetaminophen and ibuprofen.

18. A composition according to claim 15 wherein said albuterol is greater than 99% by weight R(-)albuterol.

Remarks

The claims have been amended to include the amount (in functional terms) of the components to be included and to clarify the proportion of albuterol that is present as its R-isomer. Support for claim 16 is found on page 5, line 14; support for claim 17 is found on page 5, line 15 to line 16. Claim 18 replaces former claim 14 and makes it properly dependant on newly introduced claim 15.

Claims 1 to 6, 8, 9, 13 and 14 were presented in the application as filed. Claims 9, 13 and 14 have been cancelled and claims 15 through 18 have been added. Claims 1 to 6, 8 and 15 to 18 are therefore presently pending in the application.

Claims 1 to 6 and 8 stand rejected under 35 U.S.C. 103 as obvious over Chemical Abstracts. Claims 1 to 5 stand further rejected under 35 U.S.C. 103 as unpatentable over Brittain et al., Hartley et al., Hawkins et al. and Buckner et al. Claims 6 and 8 stand further rejected under 35 U.S.C. 103 as unpatentable over the latter four references in view of Chemical Abstracts. These rejections are traversed, and reconsideration is requested, for the following reasons:

The thrust of applicants' invention is the treatment of asthma while reducing the side effects associated with the administration of racemic albuterol. Side effects of drugs which, like albuterol, have a predominant β_2 agonist component, can arise from four presently recognized interactions, as discussed in the declaration under 37 C.F.R. 1.132 by Dr. Gunnar Aberg submitted herewith and rephrased below:

(a) non-adrenergic effects (there is no evidence for this among the references cited in the present case);

(b) interaction of the β-agonist with α receptors; (Second generation β-agonists like albuterol are relatively free of this problem.)

(c) interaction of the primarily β_2-agonist drug with β_1 receptors; and

(d) interaction of β_2-agonists with β_2 receptors giving rise to tachyphylaxis and perhaps to sensitization and CNS effects, such as excitement and hyperkinesia.

Tachyphylaxis in response to albuterol has been demonstrated in airways [See Passowicz Muszynska Index Medicus Abstr. 91164287 (1991) (Attachment A); and Pauwels Index Medicus Abstr. 86051970 (1986)] (Attachment B). Sensitization has likewise been reported [See Chapman et al. Brit. J. Pharmacol. 99, 66P (1990)] (Attachment C). The mechanisms of these side effects are not clear and may not be the same.

The Brittain, Hartley, Hawkins and Buckner references all address the comparative interaction of albuterol isomers with β_1

vs β_2 receptors, a type (c) interaction according to the definition above. Three of these references show that there is perhaps some slight potency advantage to the use of pure R(-) albuterol vs. racemic albuterol (although Hartley shows a potency advantage to racemic albuterol), but none shows that there is any β-selectivity advantage to R over S or over racemic. On the contrary, Buckner concluded that the ratios of tracheal (β_2) to atrial (β_1) activities of R and S are indistinguishable. Side effects that are based on type (c) interactions arise from differences in receptor selectivity, and the person of ordinary skill would conclude from the teachings of these four references that there is no advantage of R over racemic in terms of expected amelioration of side effects. The Aberg Declaration establishes that the references by Brittain, Hartley, Hawkins and Buckner do not teach any expectation of decreased side effects from the administration of the pure R isomer as compared to the racemate.

Thus, at the time of filing of applicants' parent application (1/5/90), there were no teachings among the references cited that would motivate a person of ordinary skill to administer the pure R(-) isomer of albuterol for the treatment of asthma on the basis of its receptor selectivity.

What about potency? Even though applicants' disclosure does not relate to potency, does the art nonetheless encourage the person of ordinary skill to resolve and administer pure R albuterol on the basis of potency? Unless one pure enantiomer antagonizes the effects of the other, the theoretical advantage of a pure enantiomer is at most two-fold. A racemate, being a 50:50 mixture, simply acts like half a dose of the pure enantiomer and half a dose of filler. Because chemical resolution of racemic mixtures is never 100% efficient, a resolution will always yield less than 50% of the single isomer. Thus, unless one enantiomer antagonizes the effect of the other, there is no reason to suffer the loss of material attendant upon their resolution. For example, it has been known for years that

the activity of metoprolol as a β- blocker resides in its S isomer, but no one has ever marketed pure S-metoprolol because there has been no motivation to go to the trouble of removing the R isomer.

A potency ratio significantly greater than 2 between a single enantiomer and its racemate would be consistent with antagonism by one enantiomer and would provide motivation for resolving the racemate. No such teaching is found in any of the references. Choosing the single most optimistic experimental result from among the results of three tissues in only one of the four references, one may derive a 2.3 fold potency ratio for a single (R) isomer vs racemate. This falls in the range described above for "active isomer plus filler" and provides no motivation to undertake a separation of isomers. And these are the most encouraging data selected by hindsight reconstruction; the rest of the references, taken together, fairly suggest no clear preference of one isomer. Therefore, at the time of filing, the art did not suggest using pure R(-) albuterol either for lessened side effects or for potency enhancement. This conclusion is supported by the Declaration of Dr. Aberg. (The articles referred to by Dr. Aberg which have not been previously cited in this Application are included with the Declaration of Dr. Aberg as Exhibits 1, 2 and 3.)

Applicants disclose an unexpected diminution in side effects when the pure R isomer is administered. In support of this, applicants now cite two publications by the group of Morley and Chapman which appeared subsequent to the filing of the application: Morley, Chapman et al. Brit. J. Parmacol. 104 Suppl, 295P (1991) and Chapman et al. Trends in Pharmacol. Sci. 13 231-232 (1992). The significance of their disclosures is discussed in the Declaration by Dr. Aberg and copies are enclosed for the convenience of the Examiner as Exhibits 2 and 3. In these papers, the first of which was presented at a conference in September 1991, Morley et al. address the question of a distinction between a single enantiomer and racemic albuterol in

a type (d) interaction, thus supporting the concept of lessened side effects by the administration of pure R isomer.

The Morley and Chapman references disclose that the S(+) isomer in bronchial tissue causes a hypersensitivity to allergen. The authors conclude from their experiments that the desired bronchodilator effect (due to the R isomer) is prone to tachyphylaxis, while the undesired hypersensitivity (due to the S isomer) is less prone to tachyphylaxis. The authors state "It has long been recognized that use of sympathomimetics for asthma therapy is associated with a range of inconsistent or frankly paradoxical effects....our findings indicate that it may be prudent to remove enantiomers that were previously thought to be biologically inert." (Chapman et al. p. 232) Thus, the use of the pure R isomer is concluded to provide unexpected advantages. Applicants' disclosure of removing the S isomer so as to reduce side effects, and claims directed thereto, dating to at least January 1990 are novel and nonobvious -- particularly as evidenced by the subsequent Morley and Chapman publications.

For the foregoing reasons the rejections of claims 1-6 and 8 under 35 U.S.C. 103 are believed overcome. Reconsideration and withdrawal of the rejections are requested.

Claims 9, 13 and 14 which had been rejected under 35 U.S.C. 112 are now cancelled. Claim 15, which replaces claim 9, now clarifies that the pharmaceutical composition comprises from 90 to 100% of the R isomer. The Examiner had also asserted that former claims 9, 13 and 14 were too broad, absent recitation of amounts of ingredients. The claims have been amended to incorporate in functional terms the amounts of the ingredients. That such functional language is definite, allowable and common practice in the pharmaceutical art is illustrated in U.S. patents 4,975,426, claim 1, 4,923,898, claim 1 and 5,025,019, claim 1, copies of which are included for the convenience of the Examiner as attachments D, E and F, respectively. The rejections under 35 U.S.C. 112 are therefore believed overcome, and reconsideration and withdrawal is requested.

There being no further issues the application is believed in condition for allowance and such is requested.

Respectfully submitted,

Richard W. Wagner

Richard W. Wagner
Agent for Applicants
Registration No. 34,480

Lexington, MA 02173.
Dated: February 10, 1993

EXHIBIT 12

DOCKET NO. SPC89-05'

#24
3/18/93

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Timothy J. Barberich and James W. Young

Serial No.: 07/896,725 Group Art Unit: 1205

Filed: June 9, 1992 Examiner: L. Schenkman

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

93 MAR -9 AM 6:31

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231 on 3/10/93

Hamilton, Brook, Smith & Reynolds, P.C.

A. J. Harris 3/10/93
Signature Date

DECLARATION

To: Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, Gunnar Aberg, declare:

THAT I am a citizen of Sweden and a resident of the Town of Westborough, Worcester County, Massachusetts;

THAT I am Vice-President of Research and Development, Pharmaceutical Division, Sepracor, Inc., Marlborough, Massachusetts. From 1968 to 1973 I was Director of Pharmacology at Bofors-Nobel Pharma, from 1974 to 1978 I was Group Leader in General Pharmacology at AB Haessle, from 1978 to 1980, I was Director of Pharmacology at Astra Pharmaceuticals, from 1980 to 1982 I was Director of

Cardiovascular Pharmacology at Ciba-Geigy; and from 1982 to 1988 I was Director of Pharmacology, and from 1988 to 1992 Executive Director of Pharmacology, at Bristol-Myers Squibb;

That I am a graduate of the University of Linkoping, Sweden from which I hold a Ph.D. in Pharmacology and of the University of Goteborg, Sweden from which I hold a Ph.D. in Zoophysiology, and that I am an Associate Professor in Applied Pharmacology at the University of Linkoping, Sweden;

That I have twenty-eight years' industrial experience in the area of pharmacology research;

That I am an author of 86 articles on pharmacology, including eight articles on adrenergic β-blockers and β-agonists and that I am an inventor on seven U.S. patents and 6 pending U.S. applications and that I have made numerous presentations before professional societies on the subject of adrenergic drugs;

That I have reviewed carefully the Office Action dated August 10, 1992 in the above case. I have also reviewed the application in the above case and the art cited by the examiner in his rejection, namely Chemical Abstracts 89:123259m (1978), Brittain et al., Harley et al., Hawkins, et al. and Buckner et al.; and as a result of my review and general knowledge of the subject area, I make the following analysis:

The Chemical Abstracts reference teaches that racemic albuterol may be used to treat asthma, but there is no teaching in the reference that would motivate one skilled in the art to go to the considerable trouble and expense of isolating and administering either enantiomer.

Brittain et al. show that both enantiomers and the racemic mixture of albuterol are very selective for β_2 receptors, but the isomeric activity ratio of R and S albuterol on isolated tracheal muscle (β_2) vs atrial muscle (β_1) is "impossible to calculate...because the isomers are virtually inactive on this tissue." R(-) and racemic albuterol inhibited acetylcholine-induced bronchospasm in

anesthetized guinea pigs at dose-levels of 2.5 to 100 µg/kg. The corresponding figure for S(+) albuterol was 50 to 5000 µg/kg, indicating, as expected, a lower potency of the S-isomer. No difference was reported between the effects of R(-) and R,S albuterol in the anesthetized guinea pig. The potency ratio of R(-) vs racemic albuterol could be calculated when the compounds were tested in a model of acetylcholine-enhanced pulmonary resistance in the dog, and indicated that the R(-)-isomer was approximately twice as potent as the racemate. On the isolated guinea pig trachea, Brittain et al. found R-albuterol to be approximately equipotent with the racemate (table 1; page 146). Thus, from a study of the Brittain et al. reference I have not been able to conclude anything definitive regarding either (1) the selectivity of the R isomer vs the racemate, or (2) the relative potencies of the two compounds.

Hartley and Middlemiss teach that both isomers and the racemic mixture of albuterol act on β_2 receptors rather than β_1 receptors. The effects of the R isomer and the racemic mixture are equiactive on β_2 receptors of the intact guinea pig trachea; indeed, it can be calculated from the reported data that the racemate is 1.5 times as potent as the R(-) isomer. There is no clear teaching with regard to selectivity between β_1 and β_2 for the two isomers and the racemate, because the ratio of trachea vs left atrium activity is roughly the same for the R isomer and for the racemate, and the ratio of trachea to right atrium shows a better ratio for the R isomer but partial agonist activity for the R isomer and not for the racemate. Thus, no conclusion can be drawn from Hartley and Middlemiss as to whether the R isomer would enjoy any advantage over racemic albuterol in terms of side effects.

Hawkins and Klease characterize the study of Hartley and Middlemiss by stating that Hartley reported that racemic albuterol was 1.5 times as active as the minus enantiomer. In their studies, Hawkins and Klease found that the R enantiomer was approximately twice as potent as the racemate. They did

not examine any tissue other than guinea pig trachea so that no conclusion relating to relative selectivity could be drawn. Thus if one ignored the teachings of Brittain et al. and particularly of Hartley et al., one could interpret the Hawkins publication to disclose a small potency advantage for the R isomer. On a theoretical basis if the S isomer were totally inactive, the racemate (being a 50-50 mixture) should have a theoretical potency of about 50% that of the R isomer; Hawkins' results would be consistent with that hypothesis.

The study by Buckner and Abel examines the ratio of activity of the R and S isomers of albuterol in guinea pig atria and guinea pig trachea. They concluded "even though the potencies of single isomers may differ as much as twenty-four fold between atria and trachea, the stereoselectivity for production of activity is the same." That is, the selectivity, as measured by the ratio of tracheal to atrial activity, is the same for the two isomers. Buckner did not examine racemic albuterol so no conclusion can be drawn as regards any potency advantage of a single pure R isomer vs the racemate.

The combined teachings of all of the foregoing references provide little clear direction. If one ignores Hartley and one of Brittain's experiments, with the intention of selectively extracting from the references any advantage associated with the R isomer, it appears that the R isomer may enjoy a theoretical two-fold potency advantage over the racemate. However, as a practical matter, even were this the case, it would not motivate a person of scientific skill and experience in the pharmaceutical industry to prepare and administer the pure R isomer instead of the racemate. This is because a process for the resolution of racemic albuterol would inevitably produce R albuterol in less than 50% yield, whereas the use of the racemic albuterol would, at worst, provide 50% of the potency of the pure R. Thus there is little to be gained by resolving the racemate.

As regards the question of diminution of side effects of

R-albuterol vs racemic albuterol, there is no clear teaching in any of the references that R-albuterol would enjoy an advantage over racemic albuterol on the basis of its selectivity between β_1 and β_2 receptors.

In the instant application, Barberich and Young disclose an unexpected diminution in side effects when the pure R isomer of albuterol is administered. Side effects of drugs that have a predominant β_2 agonist component can arise from four presently recognized and well characterized receptor interactions: (a) non-adrenergic effects; (b) interaction of the β-agonist with α-receptors; (c) interaction of the β_2 agonist with β_1 receptors; and (d) interaction of the β_2 agonist with β_2 receptors. The interactions of these drugs with β_3 receptors (the adipocyte β-receptors) have not been well defined and are therefore not discussed in this declaration. Non-adrenergic effects can be triggered by interaction with any of the hundreds of other receptors and by non-receptor interactions, and they can originate from portions of the drug molecule outside the β_2 pharmacophore. They are, for this reason, difficult to predict or screen for. Interaction of β-agonists with α-receptors are known in epinephrine but are not of clinical significance in agonists like albuterol. Interaction of β_2 agonists with β_1-receptors, causing pulmonary agents to exhibit cardiac side effects, is well documented for isoproterenol and has been discussed above for albuterol. The literature cited in the office action provides no evidence for an advantage of either enantiomer of albuterol on the basis of β_2 vs β_1 specificity.

Interaction of β_2-agonists at β_2-receptors can give rise to tachyphylaxis and perhaps to sensitization in addition to the desired bronchodilation. While well documented, these effects are only recently beginning to be understood. Tachyphylaxis appears to arise from mechanisms that are subsequent to the receptor-ligand interaction. [See Strasser et al. Adv. Exp. Med. Biol. 231, 503-517 (1988)]

The recent publications of Morley et al. [Brit. J. Pharmacol. 104, Supp. 295P (1991)] and Chapman et al. [Trends in Pharmacological Science 12 231-232 (1992)], which I have also reviewed, provide newly available support for applicants' disclosure in this respect. The Morley and Chapman references disclose that the S(+) isomer in bronchial tissue causes a hypersensitivity to allergen. This hypersensitivity is not usually observed in acute administration because the bronchodilator effect of the R enantiomer masks the hypersensitivity. However, on subchronic treatment with racemic albuterol Morley et al. were able to detect the hypersensitivity. They concluded from their experiments that the desired bronchodilator effect was prone to tachyphylaxis while the undesirable hypersensitivity is less prone to tachyphylaxis. Indeed, in the Chapman et al. paper the authors recommend that it may be prudent to remove enantiomers that were previously thought to be biologically inert. Their results support a previously undisclosed advantage to the use of pure R enantiomer in that the side effect of paradoxical hypersensitivity is likely to be ameliorated.

I further declare that all statements of the foregoing declaration made of my own knowledge are true and that those made upon information and belief are believed true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Signed by me this 8th day of February 1993.

Gunnar Aberg

EXHIBIT 13

SPC8905
RWP:lk
7/22/93

CP 205

PATENT APPLICATION
Docket No. SPC89-05'
Expedited Procedure under 37 C.F.R. 1.116
Examining Group 1205

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner of Patents and Trademarks
BOX AF

#28/1
(WE)
JLP
7/30/93

Applicant: Timothy J. Barberich and James W. Young

Serial No.: 07/896,725 Group Art Unit: 1205

Filed: June 9, 1992 Examiner: L. Schenkman

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

93 JUL 30 PM 2:28

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231 on July 23, 1993
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

D. J. Hamm July 23, 1993
Signature Date

Amendment After Final Action Under 37 CFR 1.116

The Honorable Commissioner
of Patents and Trademarks
Box AF
Washington, D.C. 20231

Sir:

This is in response to the official action of June 7, 1993 (Paper Number 26), which requires response by September 7, 1993.

Please amend the application as follows:

In the Claims:

Claim 18, line 2 change "R-albuterol" to -- R(-)albuterol--.

Remarks

Claims 1 to 6, 8, 9, 13 and 14 were presented in the application as filed. Claims 9, 13 and 14 were canceled and claims 15 through 18 added in applicants' response mailed to the

Patent Office on February 10, 1993. Claims 1 to 6, 8 and 15 to 18 are therefore presently pending in the application.

Claim 18 has been amended according to the suggestion of the examiner to correct a typographical error.

In the Office Action of June 7, the rejection of all of the pending claims under 35 U.S.C. §103 was reiterated and made final. In addition, the examiner indicated that the applicants' arguments of February 10 and the Aberg Declaration submitted therewith were not persuasive.

In the new discussion in paragraph 6 of the Office Action, the examiner states "Note the summary of the Brittain et al article regarding the desirability of using the R(-) isomer and its effects on β-adrenoreceptors." The Summary section in the Brittain reference does not address the "desirability" of using the R-isomer; it states that the R-isomer is more potent. Applicants have previously explained that potency does not equate with desirability; other factors must be considered. (E.g., Chloramphenicol is more potent than penicillin V, but in most cases it is not more desirable.)

Moreover, it is not understood by applicants why the teachings of Brittain are isolated and emphasized by the examiner when the equally valid teachings of Hartley and Middlemiss are available which show that the racemate is 1.5 times as potent as the R-isomer. The analysis of selected pieces of the art has been found improper by the CCPA in *In re Kuderna* (165 USPQ 575). The issue of patentability must be approached "in terms of what would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the sum of all the relevant teachings in the art." [Emphasis in original] In the previous response, applicants have analyzed the teachings of the art taken as a whole; the substance of that response is summarized below.

The thrust of applicants' invention is the reduction of side effects, which arise in the treatment of asthma with racemic albuterol, by the administration of R-(-)-albuterol in place of

racemic albuterol. Side effects of drugs which, like albuterol, have a predominant β_2 agonist component, can arise from a number of interactions, one of which is addressed by the cited prior art: interaction of the primarily β_2-agonist drug with β_1 receptors. The Brittain, Hartley, Hawkins and Buckner references address the comparative interaction of albuterol isomers with β_1 vs β_2 receptors. None of the references shows that there is any β-selectivity advantage of R over S or over racemic. On the contrary, Buckner concludes that the ratios of tracheal (β_2) to atrial (β_1) activities of R and S are indistinguishable. The earlier Aberg Declaration confirmed that the references by Brittain, Hartley, Hawkins and Buckner do not teach any expectation of decreased side effects from the administration of the pure R isomer as compared to the racemate.

Thus, at the time of filing of applicants' parent application (1/5/90), the references cited would not have motivated a person of ordinary skill to administer the pure R(-) isomer of albuterol for the treatment of asthma on the basis of its receptor selectivity.

The examiner has suggested that increased potency might be a basis for separating enantiomers. However, to the contrary, and mindful that applicants' disclosure does not relate to potency, the art does not encourage the artisan of ordinary skill to resolve and administer pure R albuterol on the basis of potency. The reason for this lack of encouragement is because the theoretical advantage of a pure enantiomer is at most two-fold. A racemate, being a 50:50 mixture, simply acts like half a dose of the pure enantiomer and half a dose of filler. Since chemical resolution of racemic mixtures is never 100% efficient, a resolution will always yield less than 50% of the single isomer. Thus, unless one enantiomer antagonizes the effect of the other, there is no potency-based reason to suffer the loss of material attendant upon their resolution.

A potency ratio significantly greater than 2 between a

single enantiomer and its racemate would be consistent with antagonism by one enantiomer and would provide motivation for resolving the racemate. No such teaching is found in any of the references. Therefore, at the time of filing, the art did not suggest using pure R(-) albuterol either for lessened side effects or for potency enhancement. This conclusion was supported by the earlier Declaration of Dr. Aberg.

The examiner has suggested that applicants show comparative therapeutic indices to support their contention of lessened side effects. Applicants provide herewith the Declaration of Dr. Gunnar Aberg to establish that the results of Chapman and of Morley, in view of additional studies now performed by applicants, would indicate to the person of skill in the art that the R-isomer would have a higher therapeutic index in humans than would the racemate. The tests are accepted in the art as being predictive of efficacy in treating humans, and the pending method of use claims are narrowly drawn to the specific use for which the tests are predictive. (See *Ex parte Chwang*, 231 USPQ 751). Thus, as a matter of law, an adequate showing has been made to support patentability of the pending claims.

The examiner has further cautioned the applicants that a showing, if made, might not be persuasive in light of *In re Adamson*. In *Adamson*, the CCPA held that in establishing that one isomer was more potent, the applicants had "done no more than is suggested by the prior art and have ascertained no more than what would be expected by one skilled in the art." [Emphasis added] In the present case, applicants have shown that the art, taken as a whole, does not suggest that the resolution of the racemate and the use of R-(-)-albuterol substantially free of its S-isomer would provide therapy for asthma while simultaneously reducing side effects. Thus, the demonstration of improved therapeutic index by applicants should be persuasive in light of *In re Adamson*.

For the above stated reasons, applicants believe that the rejections under 35 U.S.C. §103 have been overcome. Applicants

respectfully request reconsideration of the application and allowance thereof. If the examiner feels that a telephone conversation would expedite prosecution of this application, he is asked to call applicants' agent at (617) 861-6240.

Respectfully submitted,

Richard W. Wagner

Richard W. Wagner
Agent for Applicants
Registration No. 34,480
(617) 861-6240

Lexington, MA 02173

Dated: July 23, 1993

EXHIBIT 14

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Timothy J. Barberich and James W. Young

Applicant's Docket No.: SPC89-05 Group Art Unit: 1205

Filed: Examiner:

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

To: Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

PRELIMINARY REMARKS

Dear Sir:

This application is a file wrapper continuation of our earlier application, serial number 07/896,725 which is itself a continuation of application serial number 07/461,262.

Status of Claims

Claims 1 to 12 were presented in the '262 case as originally filed. Claims 7, 10, 11 and 12 were canceled and claims 13 and 14 were added in the response of September 23, 1991 in the '262 case. Claims 9, 13 and 14 were canceled and claims 15, 16, 17 and 18 were presented in the response of February 10, 1993 in the '725 case. Claims 1 to 6, 8 and 15 to 18 are therefore presently pending in the application. Three of these are independent claims (claims 1, 6 and 15).

All of the claims were rejected in the final action of June 7, 1993 (paper number 26) and the rejection was maintained in two subsequent advisory actions (papers 30 and 32). Thus, the status of the claims at the end of prosecution in the parent ('725) case was as follows:

Allowed Claims	Claims Objected To	Claims Rejected
None	None	1 to 6, 8, 15 to 18

Status of Amendments

An amendment was proffered in applicants' response of July 23, 1993, but it was not entered. The amendment is not believed necessary for further prosecution and has not been subsequently presented.

Summary of the Invention

Applicants' invention is directed to a method of treating asthma and reducing the undesirable side effects associated with racemic albuterol by using the R isomer of albuterol substantially free of the S isomer. R-albuterol may be combined with a bronchodilator, antihistamine or analgesic. Methods and pharmaceutical compositions relating to the combination also fall within the inventive concept.

The administration of β-agonists for the treatment of asthma is commonly accompanied by undesirable side effects. Evidence suggests that β_2-agonists may make asthma worse, perhaps by increasing airway hyperresponsiveness to spasmogens. This gives rise to the most serious of the side effects associated with the use of β-agonists to treat asthma: death from asthma. In this regard, Spitzer et al. [New England Journal of Medicine 326, 501-506 (1992)] have shown that racemic albuterol, taken by metered dose inhaler, was associated with an increased risk of death from asthma or near fatal asthma. When the odds ratio was calculated with adjustment for all factors, the increase in risk (to an odds ratio of 2.8) was clinically important and statistically significant.

Applicants have surprisingly found that, with regard to hypersensitivity, there is an unexpected advantage to the use of the pure R isomer. Applicants have shown (see the declaration of Gunnar Aberg accompanying the response of July 23, 1993) that the S isomer causes a hypersensitivity to allergen and that the desired bronchodilator effect due to the R isomer is prone to tachyphylaxis (desensitization), whereas

the undesired hypersensitivity arising from the S isomer is less prone to tachyphylaxis. This means that, in order to achieve bronchodilation, a patient in chronic treatment requires ever-increasing doses of racemic albuterol. While greater and greater doses of R-albuterol are needed to provide the desired bronchodilation, the accompanying greater and greater doses of S-albuterol dramatically increase the patient's susceptibility to asthmatic attack. Similar results have appeared, subsequent to applicants' invention, in two independent publications from other labs [Morley et al., British Journal of Pharmacology, 104, Supplement, 295P (1991) and Chapman, et al. Tran. In Pharm. Science 13, 231-232 (1992)]. Thus, by eliminating the S-isomer and its undesirable hypersensitization, applicants have found an unexpected benefit to the use of the pure R isomer for the treatment of asthma.

Issues

1. In the office action of June 7, 1993, a final rejection in the parent case, the examiner rejected claims 1 to 6 and 15 to 18 over Chemical Abstracts 89:123259m for "reasons of record." The reasons of record are found in the office action of August 20, 1990, in which the examiner states that the reference teaches the use of albuterol to treat asthma and that it is his position that the determination of a particular isomer to employ would be a matter of obvious alternatives to one skilled in the art.

2. The examiner also rejected claims 1 to 5 as unpatentable under 35 U.S.C. §103 over Brittain et al. [Brit. J. Pharmacol. 48, 144-147 (1973)], Hartley et al. [J. Med. Chem. 14, 895 (1971)] and Buckner et al. [JPET 189, 616-625 (1974)]. These references are relied upon to teach "the greater bronchodilation activity of the R isomer over the S isomer."

3. Claims 6, 8 and 15 to 18 were rejected under 35 U.S.C. §103 as obvious over Brittain et al, Hartley et al, and

Buckner et al, as before and further in view of Chemical Abstracts "for reasons of record." There is no "record" with regard to claims 15 to 18, which were newly presented in the response immediately preceding the rejection. One assumes from analogy to earlier office actions that the examiner takes the position that the Brittain, Hartley and Buckner references teach greater bronchodilation activity of the R isomer, and that the Chemical Abstracts reference teaches albuterol in combination with other drugs.

4. The examiner's position is that the declaration under 37 C.F.R. 1.132 of Gunnar Aberg of July 23, 1993 "failed to show unexpected activity or less undesirable side effects (e.g. comparative therapeutic indices)."

5. The examiner cited the case of *In re Adamson* [125 USPQ 233] for the proposition that a showing of unexpected activity in a Rule 132 declaration might not overcome his obviousness rejection.

Argument

Issue 1 - The rejection of claims 1 to 6 and 15 to 18 over Chemical Abstracts 89:123259m.

The Chemical Abstracts reference is directed to a comparison of bronchodilator effects of racemic albuterol and drug combinations incorporating racemic albuterol. The reference does not teach or suggest the use of an optically pure isomer of albuterol either alone or in combination. Arguably, the reference teaches away from the use of a single isomer to reduce side effects: it states, "a combination of salbutamol [albuterol] and hydroxyzine seems, therefore, to be one rational means of treating asthma with fewer side effects than the salbutamol-hydroxyzine-theophylline mixture, but still about the same effectiveness." Thus, the goal of the reference appears to be to lower the side effects associated with albuterol. However, rather than separate the enantiomers and use one enantiomer, as taught by applicants, (which the

examiner has alleged would be obvious) the authors turned instead to modulating components of the mixture.

The examiner's position that "the determination of a particular isomer to employ would be a matter of obvious alternatives" is only true if it is obvious that the use of a single isomer provides an advantage. That teaching is entirely missing from the reference. In this regard, it is worth noting that the mere fact that enantiomers exist does not render the use of a particular enantiomer obvious. In order to use an enantiomer, one must first prepare or isolate the single pure enantiomer. Because chemical resolution of a racemic mixture is never 100% efficient, a resolution will always yield less than 50% of the single isomer. Chiral syntheses are similarly expensive and/or inefficient. As stated by others (e.g., European patent application 256586, page 2, line 8) "a major reason for the continued use of mixtures of stereoisomers is that the cost of separation of the stereoisomers exceeds the potential advantage of a possible increase in activity." It would not have been obvious to prepare and use optically pure R-albuterol because there is no suggestion of any advantage of R-albuterol in the reference.

Issue 2 - The rejection of claims 1 to 5 as obvious over Brittain et al., Hartley et al. and Buckner et al.

Brittain et al. show that both enantiomers and the racemic mixture of albuterol are very selective for β_1 receptors, but the isomeric activity ratio of R- and S-albuterol on isolated tracheal muscle (β_2) vs atrial muscle (β_1) is "impossible to calculate...because the isomers are virtually inactive on this tissue." The potency ratio of R(-) vs racemic albuterol in β_2 receptors as measured by acetylcholine-induced bronchospasm in anesthetized guinea pigs is 1.28, in acetylcholine-induced pulmonary resistance in anesthetized dogs is 2.3 and on isolated guinea pig trachea is

0.90 (i.e. the racemate is 1.1 times as potent as the R isomer). Thus, from a study of the Brittain reference one may conclude nothing definitive regarding either the selectivity of R vs racemic or of the potency of R vs racemic.

Hartley and Middlemiss teach that both isomers and the racemic mixture of albuterol act on β_2 receptors rather than β_1 receptors. The effects of the R isomer and the racemic mixture are equiactive on β_2 receptors of the intact guinea pig trachea and indeed the racemate is reported to be 1.5 times as potent as the R isomer. There is no clear teaching with regard to selectivity between β_1 and β_2-receptors, which might indicate the potential for side effects. Thus no conclusion can be drawn from Hartley and Middlemiss as to whether the R isomer would enjoy any advantage over racemic albuterol in terms of side effects.

The study by Buckner and Abel examines the ratio of activity of the R and S isomers of albuterol in guinea pig atria and guinea pig trachea. They concluded "even though the potencies of single isomers may differ as much as twenty-four fold between atria and trachea, the stereoselectivity for production of activity is the same." That is, the selectivity, as measured by the ratio of tracheal to atrial activity, is the same for the two isomers. Buckner did not examine racemic albuterol, so no conclusion can be drawn as regards any potency advantage of a single pure R isomer vs the racemate.

In an earlier office action (December 9, 1991) the examiner had rejected the same claims over an additional reference by Hawkins et al. [J. Med. Chem. 16, 856-857 (1973)]. Although the rejection over Hawkins was not maintained in the final office action, it appears pertinent to the substance of the rejection, which might otherwise lack a balanced consideration of the art. In their studies, Hawkins et al. found that the R enantiomer was 2.15 times as potent as the racemate. They did not examine any tissue other than guinea pig trachea so that no conclusion relating to relative

selectivity could be drawn.

The issue of patentability must be approached "in terms of what would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the sum of all of the relevant teachings in the art ..." [*In re Kuderna* (165 USPQ 575)]. There are two teachings that could have rendered the use of R-albuterol obvious: (1) a teaching that it is more than twice as potent as the racemate (which would indicate that the S-isomer's activity is antagonistic to the R-isomer's potency); or (2) a teaching that fewer side effects are associated with the R isomer. Neither of these teachings is found in any of the references. However, the art is not silent on what the person of skill ought to expect; it teaches that there is nothing to be gained, either in potency or side effects, by resolving the racemic albuterol. Hawkins et al. and Buckner et al. appear to indicate that the R isomer is about twice as potent as the racemate (which merely indicates that the S-isomer is inert); Hartley et al. teaches that the racemate is about 1.5 times as potent as the R isomer (which would indicate that the S-isomer has some therapeutic potency); Brittain et al. indicates that one or the other isomer is more potent, depending on the test. There is a certain lack of agreement among the references concerning the relative potency of the R isomer and the racemate, and the person of ordinary skill in the art would be, at least, confused by the cited references.

If one ignores some of the references, it appears that the R isomer may enjoy a theoretical twofold potency advantage over the racemate. However, even assuming that R-albuterol is twice as potent as the racemate, this would not motivate a person of skill and experience in the pharmaceutical industry to prepare and administer the pure R isomer. This is because, as discussed above, a process for the resolution of racemic albuterol would inevitably produce R-albuterol in less than 50% yield, whereas assuming that S-albuterol is totally inert ballast, the use of the racemic albuterol would, at worst,

provide 50% of the potency of the pure R. Thus there is nothing to be gained by resolving the racemate. A potency ratio significantly greater than two between a single enantiomer and its racemate would be consistent with antagonism by one enantiomer and would provide motivation for resolving the racemate. However, no such teaching is found in any of the references, even when viewed selectively. Therefore at the time of filing, the art did not, on the basis of potency, suggest any practical advantage to using pure R albuterol.

A second basis for separating enantiomers would be to provide lessened side effects. Indeed, the unexpected diminution in side effects when the pure R isomer of albuterol is administered is the basis of the instant application, but it is not suggested by any of the references. As explained in the July 23, 1993 declaration of Gunnar Aberg, side effects of drugs that have a predominant β_2 agonist component can arise from four presently recognized interactions: (a) non-adrenergic effects; (b) interaction of the β-agonist with α-receptors; (c) interaction of the β_2 agonist with β_1 receptors; and (d) interaction of the β_2 agonist with β_2 receptors.

(a) Non-adrenergic effects can be triggered by interaction with any of the hundreds of other receptors and by non-receptor interactions, and they can originate from portions of the drug molecule outside the β_2 pharmacophore. They are, for this reason, difficult to predict or screen for. Applicants are aware of no teachings in the literature of relative liabilities of racemate or enantiomers of albuterol as regards non-adrenergic effects, and theoretically such differences would be improbable.

(b) Interaction of β-agonists with α-receptors are known in first generation adrenergics but are not generally of clinical significance in second generation agonists like albuterol. Likewise,

applicants are aware of no art that would suggest any distinction between racemate and enantiomers on this basis.

(c) The interaction of β_2 agonists with β_1 receptors, causing pulmonary agents to exhibit cardiac side effects, is well documented and has been discussed above for Brittain, Hartley, Buckner and Hawkins. The literature cited provides no evidence for an advantage of either enantiomer of albuterol on the basis of β_1 vs. β_2 specificity.

(d) The fourth interaction, β_2 agonists acting at β_2 receptors giving rise to tachyphylaxis and sensitization, is known but not described in any of the references cited for albuterol.

Thus, in January of 1990 when the grandparent of the present application was filed, there was no teaching in the art that the use of pure R-albuterol enjoyed any advantage in diminution of side effects.

Issue 3 - The rejection of claims 6, 8 and 15 to 18 over Brittain et al, Hartley et al, Buckner et al and Chemical Abstracts.

The inadequacy of Brittain, Hartley and Buckner to support the rejection of applicants' claims to the use of R-albuterol has been presented above. The addition of the Chemical Abstracts reference, while indicating that racemic albuterol has been used with other drugs, does not supply the missing teaching regarding the advantage of the use of the R isomer in diminishing side effects.

Issue 4 - The setting aside of the Declaration of Dr. Gunnar Aberg.

Accompanying the response of July 23, 1993, applicants provided a declaration from Dr. Gunnar Aberg to establish that

his results and those of Chapman and of Morley would indicate to the person of skill in the art that the R isomer would have a higher therapeutic index in humans than would the racemate. Dr. Aberg averred that the tests relied on as evidence are accepted in the art as being predictive of efficacy in treating humans; the pending method of use claims are narrowly drawn to the specific use for which the tests are predictive. [See Ex parte Chwang (231 USPQ 751).] Dr. Aberg's credentials were presented in the declaration and his conclusions as to side effects and unexpected activity cannot be set aside by the examiner without some basis for so doing. None was presented. Therefore it is presumed that the declaration is accepted for what it teaches; namely, that a person of skill in the art would accept the studies in guinea pig trachea and the experiments of Chapman et al. and Morley et al. (described below) as predictive of a higher therapeutic index for R-albuterol. Applicants believe that the examiner's position that the declaration "failed to show unexpected activity or less undesirable side effects" cannot be maintained.

Dr. Aberg described experiments carried out in his laboratory in which isolated tracheal muscle preparations were subjected to graded doses of a spasmogen. It was found that the contractile response to the spasmogen was significantly increased in bronchial tissue strips that had been incubated with S-albuterol. No such effect was seen in the tissues that had been incubated with R-albuterol. Dr. Aberg concluded that the increased sensitivity to spasmogens from treatment with S-albuterol was due to a direct effect on bronchial smooth muscle.

Subsequent to the filing of applicants' original application, Morley et al. (op. cit.) and Chapman et al. (op. cit.) independently disclosed that the S isomer in bronchial tissue causes a hypersensitivity to allergen. Chapman et al. stated, "It has long been recognized that the use of sympathomimetics for asthma therapy is associated with a range

of inconsistent or frankly paradoxical effects...our findings indicate that it may be prudent to remove enantiomers that were previously thought to be biologically inert." Thus Morley and Chapman came to the same conclusion as applicants' original disclosure, and did so with the same understanding of the prior art as a whole: namely, that no expectation of an improved side effect profile was previously attached to the use of a single enantiomer.

In the period since the final office action of June 7, 1993 in the parent case, additional support for the conclusions drawn in the Aberg declaration has come to the attention of applicants. British patent application 2,255,503, filed more than a year after applicants' '262 application, discloses that the long standing problems inherent in therapy with albuterol and other β_2 sympathomimetic bronchodilators may unexpectedly be ameliorated by the expedient of administering the drug not, as hitherto, in the form of a racemic mixture, but as the R isomer (page 8, line 25 to line 33 of the copy enclosed). The problems that may be avoided are enumerated on page 12. A series of experiments is disclosed at page 15 to page 16 in which guinea pigs were challenged with intravenous histamine after intravenous infusion of S-albuterol or vehicle. The results indicated a profound hypersensitivity induced by S-albuterol. The British application comes to the same conclusion as did Dr. Aberg in his declaration: subjects receiving R-albuterol will exhibit a lessened tendency to hyperreactivity with equivalent benefit in terms of bronchodilator action (see page 24, line 3 to line 8 of GB 2,255,503).

This evidence of unexpected activity cannot, as a matter of law, be disregarded by the examiner. [*In re Merck*, 231 USPQ 375, 380 (Fed. Cir. 1986)]

Issue 5 - The applicability of the decision *In re Adamson*.

In the office action of June 7, 1993, the examiner indicated that no showing (even if applicants have made one)

would be persuasive in view of the decision *In re Adamson*. Although *In re Adamson* teaches that optical isomers *per se* are normally obvious over the corresponding known racemate, the decision should not be extended to stand for the proposition that a new method for using an isomer is unpatentable, particularly where, as here, the method unexpectedly provides an improved therapeutic ratio. For example, the claims of U.S. patent 4,851,444 (to Sunshine et al.) cover a method for using *S*-(+)-ibuprofen for onset-hastened analgesia, although (S)-ibuprofen *per se* was well known at the time of filing the application for a new use.

In *Adamson*, the CCPA held that in establishing that one isomer was more potent, the applicants had "done no more than what is suggested by the prior art and have ascertained no more than what would be expected by one skilled in the art" [Emphasis added]. Applicants' showing goes far beyond the evidence of enhanced potency at issue in *Adamson*. In the present case, applicants have shown that the resolution of the racemate and the use of R-(-)-albuterol substantially free of its S-isomer would provide therapy for asthma while simultaneously reducing side effects. As explained above, this is not suggested by the prior art. To the contrary, the art suggests that there would be no reduction in side effects. Thus, the decision in *Adamson* has no bearing on the patentability of this application.

Respectfully submitted,

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Dated: December 7, 1993
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EXHIBIT 15

#9

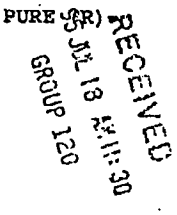
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/335,480 Group Art Unit: 1205

Filed: November 7, 1994 Examiner: Henley III, R.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R) ALBUTEROL



CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, June 9, 1995.

Philip E. Hansen
Agent for Applicant
Reg. No. 32,700

Date of Signature: June 9, 1995

Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE UNDER 37 C.F.R 1.111

Dear Sir:

This is in response to the Official Action of March 9, 1995 (Paper No. 7). The three-month period for response expires June 9, 1995; this response is therefore timely filed.

AMENDMENTS

Please amend the application as follows:

In the specification:

Page 1, line 2 (following the title and preceding the "Description"), please delete "This application is a continuation of application Serial No. 08/163,581, filed 12/7/93." and replace with

A

-- Cross Reference to Related Applications

This application is a continuation of application Serial No. 08/163,581, filed December 7, 1993 and now U.S. Patent 5,362,755, which was a continuation of application Serial No. 07/896,725, filed June 9, 1992, now abandoned, which was a continuation of application Serial No. 07/461,262 filed January 5, 1990, now abandoned.--

In the claims:

Cancel claims 5, 7 and 9-12.

Amend claims 1 and 6 as follows:

1. (once amended) A method of treating an acute attack of asthma [in an individual with albuterol], while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to [the] an individual suffering from an acute attack of asthma a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

6. (once amended) A method of treating an acute attack of asthma [in an individual with albuterol], while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to [the] an individual suffering from an acute attack of asthma a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

REMARKS

The specification has been amended to clarify that it claims priority of the great grandparent application and to fully characterize the intervening applications. The claims have been amended to clarify the invention sought to be patented in the present application. The claims have been amended so that they parallel the allowed claims in parent application Serial No. 08/163,581 (Now U.S. Patent 5,362,755); the sole difference is that the claims in the parent related to reducing side effects upon chronic administration and the instant claims relate to reducing side effects associated with acute administration. Support for the amendment is found on page 4, line 4 to line 13. The reference to the administration of albuterol to an individual "after onset of asthma to reduce breathing difficulty" (line 7) reflects acute medication, whereas the reference to prophylactic treatment (line 10) relates to chronic therapy.

Claims 1-12 were presented in the application as filed. Claims 5, 7 and 9-12 are canceled by amendment above. Claims 1-4, 6 and 8 are therefore pending in the application.

In the Office Action of March 9, 1995, all of the claims were rejected as obvious over Muittari et al. (CK) in view of Brittain et al. (CB), Hawkins et al. (CD) and Hartley et al. (CC). The rejection is traversed. Applicants' position on what the cited art fairly teaches was presented in their Preliminary Remarks, submitted December 7, 1993, in the parent case and reiterated below.

The Muittari reference is directed to a comparison of bronchodilator effects of racemic albuterol and drug combinations incorporating racemic albuterol. The reference does not teach or suggest the use of an optically pure isomer of albuterol either alone or in combination. Arguably, the

reference teaches away from the use of a single isomer to reduce side effects: it states, "a combination of salbutamol [albuterol] and hydroxyzine seems, therefore, to be one rational means of treating asthma with fewer side effects than the salbutamol-hydroxyzine-theophylline mixture, but still about the same effectiveness." Thus, the goal of the reference appears to be to lower the side effects associated with albuterol. However, rather than separate the enantiomers and use one enantiomer, as taught by applicants, (which the Examiner has alleged would be obvious) the authors turned instead to modulating components of the mixture.

Brittain et al. show that both enantiomers and the racemic mixture of albuterol are very selective for β_2 receptors, but the isomeric activity ratio of R- and S-albuterol on isolated tracheal muscle (β_2) vs atrial muscle (β_1) is "impossible to calculate...because the isomers are virtually inactive on this tissue." The potency ratio of R(-) vs racemic albuterol in β_2 receptors as measured by acetylcholine-induced bronchospasm in anesthetized guinea pigs is 1.28, in acetylcholine-induced pulmonary resistance in anesthetized dogs is 2.3 and on isolated guinea pig trachea is 0.90 (i.e. the racemate is 1.1 times as potent as the R isomer). Thus, from a study of the Brittain reference one may conclude nothing definitive regarding either the selectivity of R vs racemic or of the potency of R vs racemic.

Hartley and Middlemiss teach that both isomers and the racemic mixture of albuterol act on β_2 receptors rather than β_1 receptors. The effects of the R isomer and the racemic mixture are equiactive on β_2 receptors of the intact guinea pig trachea and indeed the racemate is reported to be 1.5 times as potent as the R isomer. There is no clear teaching with

regard to selectivity between β_1 and β_2-receptors, which might indicate the potential for side effects. Thus no conclusion can be drawn from Hartley and Middlemiss as to whether the R isomer would enjoy any advantage over racemic albuterol in terms of side effects.

Hawkins et al. found that the R enantiomer was 2.15 times as potent as the racemate. They did not examine any tissue other than guinea pig trachea so that no conclusion relating to relative selectivity could be drawn.

Putting all this together: Hawkins et al. appear to indicate that the R isomer is about twice as potent as the racemate (which merely indicates that the S-isomer is inert); Hartley et al. teaches that the racemate is about 1.5 times as potent as the R isomer (which would indicate that the S-isomer has some therapeutic potency); Brittain et al. indicates that one or the other isomer is more potent, depending on the test. There is a certain lack of agreement among the references concerning the relative potency of the R isomer and the racemate, and the person of ordinary skill in the art would be, at least, confused by the cited references, but by discarding all the data that don't conform to the desired conclusion, it is possible to conclude that the R isomer may enjoy a theoretical twofold potency advantage over the racemate. The Examiner reaches this conclusion with respect to the teachings of the references in the Office Action of March 9. For the sake of the arguments below, applicants assume that the R enantiomer is twice as potent as the racemate, although they question whether the cited references establish this.

As long as S-albuterol is totally inert ballast, a two-fold potency enhancement is of no practical consequence: a process for the resolution of racemic albuterol would

inevitably produce R-albuterol in less than 50% yield, whereas the use of the racemic albuterol would, at worst, provide 50% of the potency of the pure R. Thus there is nothing to be gained by resolving the racemate. As stated in European patent application 256586 (page 2, line 8), "a major reason for the continued use of mixtures of stereoisomers is that the cost of separation of the stereoisomers exceeds the potential advantage of a possible increase in activity."

Testa and Trager [Chirality 2, 129-133 (1990)] have created a decision tree to aid in deciding whether to develop a racemic pharmaceutical or a single enantiomer. A copy of the reference is submitted herewith as Exhibit A. If it were the case that it would always be obvious to develop a single enantiomer, there would be no need for Testa and Trager's decision tree. As they make clear, the mere fact that enantiomers exist is not justification for administering a single enantiomer; moreover, even the fact that one of the two enantiomers is more potent is not determinative. They state

> "While it is abundantly clear that a racemic mixture must be considered as the mixture of two pharmacologically distinct entities, it is also clear that this view, in and of itself, does not infer any value judgement. Such judgment awaits the light of scientific fact and it is only in this context that any decision as to develop a racemate or a eutomer as a new drug is convincingly founded."

The scientific facts referred to by Testa and Trager as they relate to albuterol were shown in the cited references to result in the judgment that the racemate was the proper entity to develop, and although both enantiomers have been known in the art for 24 years, neither has ever been developed as a pharmaceutical.

In the Office Action of March 9, 1995, the Examiner cited *In re Adamson*. Although *In re Adamson* suggests that optical isomers *per se* are normally obvious over the corresponding known racemate, the decision should not be extended to stand for the proposition that a new method for using an isomer is unpatentable, particularly where, as here, the method unexpectedly provides an improved therapeutic ratio. [See, for example, U.S. patent 4,851,444 (Exhibit B), issued 29 years after Adamson, whose claims cover a method for using S-(+)-ibuprofen for onset-hastened analgesia, although (S)-ibuprofen *per se* was well known at the time of filing the application for a new use.]

In the present case, applicants claims relate to a new use, namely a method for treating asthma while simultaneously reducing side effects associated with the administration of racemic albuterol. The unexpected diminution in side effects when the pure R isomer of albuterol is administered is the basis of the instant application, and is not suggested by any of the references. [That the references singly and in combination suggest that there would be no diminution of side effects is fully argued in the Declaration Under 37 C.F.R. 1.132 of February 8, 1993, by Dr. Gunnar Aberg, submitted with the response of February 10, 1993, in the grandparent case 07/896,725. A copy of that declaration is enclosed herewith as Exhibit C, and attention is drawn to page 5.] References do exist that suggest an advantage to R-albuterol over racemic albuterol for the reduction of side effects [Morley et al. and Chapman et al., of record in the parent case], but they were published more than a year after the priority date of the instant application, and merely add support to the patentability of the claims in the parent '581 application.

In *Adamson*, the CCPA held that in establishing that one isomer was more potent, the applicants had "done no more than what is suggested by the prior art and have ascertained no more than what would be expected by one skilled in the art". In the present case, applicants have shown that the resolution of the racemate and the use of R-(-)-albuterol substantially free of its S-isomer would provide therapy for asthma while simultaneously reducing side effects. This is considerably more than is "suggested by the prior art"; on the contrary, the art suggests that there would be no reduction in side effects. In contradistinction to the premise in *Adamson*, where presumably the art is silent, in the present case the art teaches away. Thus, the decision in *Adamson* is not controlling in this situation.

Against this background in the parent case, Examiner Henley concurred with applicants that the use of R-albuterol to treat asthma while avoiding the side effects associated with chronic administration was nonobvious. However, he did not believe that applicants' showings were sufficient to support that portion of the claimed subject matter that related to side effects associated with acute administration of racemic albuterol. For that reason he would only allow claims restricted to chronic administration. Applicants now seek to complete the original breadth of the claims, and in support thereof, submit herewith the Declaration Under 37 C.F.R. 1.132 of Dr. Dean A. Handley.

The declaration of Dr. Handley establishes that by removing the S enantiomer one maintains the bronchodilatory effects exhibited by racemic albuterol for acute therapy of asthma attacks, while simultaneously avoiding or mitigating the major side effect observed in acute therapy. To summarize briefly, Dr. Handley shows that R-albuterol produces potent

and acute bronchodilation in stable asthmatic patients. The onset of action is rapid and persists for 3 hours. R-Albuterol provides acute, symptomatic treatment and relief for conditions of asthma and bronchitis. S-albuterol is essentially without effect.

On the other hand, both individual enantiomers and racemic albuterol induce sustained tremors in animals. The preclinical observations on the relative abilities of the albuterol enantiomers to provoke tremors upon single dose, acute administration were quite unexpected. Skeletal muscle tremor is one of the most common side effects of ordinary doses of all marketed β_2-agonists. The studies reported in the declaration demonstrate that, unlike the R enantiomer, the tremorigenic liability associated with the S enantiomer is not balanced by a corresponding efficacy in producing bronchodilation. This presents a clear rationale for employing the pure R enantiomer, substantially free of the S enantiomer, in acute therapy of asthma attacks. By removing the S enantiomer, one maintains the bronchodilatory effects of racemic albuterol while providing only half the tremorigenic dose.

In light of the foregoing amendments, declaration and explanation, it is believed that the claims are allowable, and reconsideration of the rejection is respectfully requested.

The Office Action of March 9, 1995, also included a rejection of claims 1-8 under the judicially created doctrine of double patenting of the obviousness type. In the parent case, over which the unamended claims were rejected, the Examiner took the position that applicants' declarations were sufficient to establish the unexpected utility of R-albuterol in avoiding side effects associated with chronic therapy, but not those side effects associated with acute therapy.

Implicit in the earlier requirement to limit the claims to chronic therapy was the assumption that the fact that effects were demonstrated in chronic therapy did not suggest that those same advantages would be observed in acute therapy. If advantages in chronic therapy would not predict advantages in acute therapy, applicants believe that by amending the claims to limit them to side effects associated with acute therapy, they have now eliminated the overlapping obvious subject matter, and the double patenting obviousness rejection would no longer apply.

Respectfully submitted,

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Dated: June 9, 1995

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EXHIBIT 16

Docket No.: 0701.027C

#14
JRP
2/22/96

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/335,480 Group Art Unit: 1205

Filed: November 7, 1994 Examiner: Henley III, R.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

APPLICANT'S INTERVIEW SUMMARY

This is a summary of an interview held November 16, 1995, with Examiner Henley in the above case. Those present at the interview were (1) Examiner Raymond Henley III, (2) John McCullough, Senior Director of Pharmacology of Sepracor, (3) Douglas Reedich, Chief Patent Counsel of Sepracor, and (4) Philip Hansen, agent of record for the applicant.

To open the interview, Mr. Hansen sketched the history of the present case, which is a divisional of application serial number 07/896,725, now US patent 5,362,755. In the parent case the same references (Muittari, Brittain, Hawkins and Hartley) were cited against the claims, and applicants made a showing which Examiner Henley felt supported the unobviousness of the method for treating with R-albuterol as chronic medication, but did not support claims to acute medication. Applicants amended the claims in the parent case to encompass only chronic administration and the case was allowed. In the meantime, applicants have carried out additional studies that they believe fully support the remainder of the original invention, acute administration, claims to which are now pending in this application.

Dr. McCullough then discussed the June 7, 1995, Declaration of Dean A. Handley, which is of record in the case. He also discussed a new study, just completed, the

results of which will be provided in a declaration that will accompany the response to the outstanding Office Action. The studies of Dr Handley had showed three things: (1) R-albuterol is the eutomer for bronchodilation in humans; (2) S-albuterol potentiates the response to spasmogen in humans 3 hours after acute administration; and (3) all three (R- S- and R,S-albuterol) are tremorigenic. The new study, investigating intracellular calcium levels, confirms the previously submitted results concerning enhancement of response to spasmogen caused by acute administration of S-albuterol. Intracellular calcium levels are known to control contractility in smooth muscle cells. Dr. McCullough found in this study that basal Ca^{2+} levels in bovine airway smooth muscle cells were affected by acute exposure of the cells to the isomers of albuterol. Cell exposure to R-albuterol decreased basal Ca^{2+} levels. Such decreases in basal Ca^{2+} are associated with relaxation of bronchial smooth muscle. Cell exposure to S-albuterol, on the other hand, increased basal Ca^{2+} levels, and such increases are associated with contraction of bronchial smooth muscle. Indeed, in about 25% of the cells exposed to high concentrations of S-albuterol ($\geq 10^{-6}$ M) spontaneous calcium oscillations accompanied by spontaneous cell shortening was observed. No such oscillations or contractions were observed in cells exposed to R-albuterol.

Dr. McCullough explained that when cells are exposed to a spasmogen such as carbachol, two phases of increased Ca^{2+} are observed: an initial phase involving a large transient increase, and a second phase involving a sustained but lesser increase. The study showed that cell exposure to R-albuterol reduced both phases. Cell exposure to S-albuterol, on the other hand, enhanced both phases. This enhancement of

intracellular calcium represents a mechanism for bronchial hyperreactivity following acute administration of S-albuterol.

There was considerable discussion as to whether the results of the studies are adequate to overcome the rejection of record. Examiner Henley indicated that he needed to be convinced that the results were truly unexpected. Dr. McCullough noted that there is nothing in the literature to suggest adverse effects arising out of the S-enantiomer. On the contrary, one skilled in the art would have believed that the effects of albuterol, adverse and beneficial alike, reside with the R-enantiomer. No significant advantages would be expected to arise out of the use of R-albuterol compared to the racemate. Applicants' studies, however, establish that use of R-albuterol provides advantages (i.e., avoidance of hyperreactivity and reduction of tremorgenicity). One reason that these advantages are significant, Dr. McCullough explained, is because the serum half life of S-albuterol in humans is longer than that of R-albuterol. Thus, when racemic albuterol is administered, the spasmogenic and tremorgenic effects of the S-enantiomer persist long after the beneficial bronchodilatory effects of the R-enantiomer have faded. On the other hand, when R-albuterol is administered, the persistent adverse effects will be reduced (in the case of tremor) or avoided (in the case of hyperreactivity).

Examiner Henley also indicated that he needed to be convinced that *In re Adamson* is not controlling. It was pointed out that a case of *prima facie* obviousness can be overcome if it is demonstrated that the claimed invention possesses sufficient unexpected properties not actually possessed by the closest prior art. *Adamson* does not purport

to change the law in this regard. Messrs. Hansen, Reedich and McCullough agreed to prepare a response that explains what one skilled in the art would expect based on the prior art, makes clear that Applicants' results are indeed unexpected, and addresses *Adamson*.

Mr. Hansen thanked Examiner Henley for his time and the interview concluded.

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
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Dated: January 24, 1996

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EXHIBIT 17

1AC GP 120

0701.027D #7A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/691,604 Art Unit: Not assigned

Filed: August 15, 1996 Examiner: Not assigned Henley

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)ALBUTEROL

MAY 29 1997

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, May 7, 1997.

Philip E. Hansen
Agent for Applicant
Reg. No. 32,700

Date of Signature: May 7, 1997

To: Assistant Commissioner for Patents
Box Non-Fee Amendment
Washington, D.C. 20231

Preliminary Amendment Under 37 C.F.R. 1.115

Dear Sir:

Prior to examination, please amend the application as follows:

In the Claims:

Cancel claims 1-12.

Please add the following claims:

13. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual

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May 7, 1997

suffering from an acute attack of asthma a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

14. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

15. A method according to Claim ~~13 or 14~~ 23, wherein the albuterol comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.

16. A method according to Claim ~~13 or 14~~ 23, wherein the albuterol comprises at least 99% by weight of the R(-) isomer and 1% or less by weight of the S(+) isomer.

17. A method according to Claim ~~13 or 14~~ 23, wherein the optically pure R(-) albuterol is administered by inhalation.

18. A method according to Claim ~~17~~ 4, wherein the optically pure R(-) albuterol is administered in an amount of about 30 μg to about 90 μg.

6 ~~19~~. A method according to Claim ~~13 or 14~~ 25 1, wherein the optically pure R(-) albuterol is administered orally.

7 ~~20~~. A method according to Claim ~~19~~ 6, wherein the optically pure R(-) albuterol is administered in an amount of about 1 mg to about 8 mg.

8 ~~21~~. A method according to Claim ~~19~~ 6, wherein the optically pure R(-) albuterol is administered as a syrup.

9 ~~22~~. A method according to Claim ~~20~~ 7, wherein the optically pure R(-) albuterol is administered as a syrup.

1 ~~23~~. A method of treating asthma, while reducing side effects associated with the administration of racemic albuterol, comprising administering to an individual suffering from asthma a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

REMARKS

The present application is a continuation of US application, serial number 08/335,480. Claims 1-12 were present in the application as filed. All claims pending in the original application are canceled by amendment above and are replaced by new claims. Claims 13-23 are therefore pending in this continuation application.

The parent application, 08/335,480, issued to US patent 5,547,994 on August 20, 1996. One week before issue, on August 13, 1996, two references were brought to the attention of applicants' undersigned representative. These references had just been provided by a potential licensee and had not been considered in the prosecution of the '480 case. Although applicants believe that the references are merely cumulative to the references already of record, they did not wish the patent to issue without explicit consideration of the additional references. In accordance with the procedures outlined in the MPEP and in accordance with advice received via telephone from the Office of Petitions, applicants immediately filed a Petition to Withdraw from Issue and a request for File Wrapper Continuation of the '480 case, so that the references could be considered. The Petition to Withdraw from Issue and fee were hand carried to the Office of Petitions on August 15, 1996.

On August 21, 1996, applicants' Petition to Withdraw from Issue was dismissed because there was insufficient time to withdraw the patent. It then became necessary to petition to have the instant application converted from a filing under 37 CFR §1.62 to a continuation under 37 CFR §1.60. A decision mailed on February 28, 1997, granted applicants' petition of August 23, 1996 to effect such a conversion. The application now before the examiner is the culmination of this process.

Claims 13-21 above are presented solely to allow the consideration of the two references not previously cited; the wording of these claims is identical to that of the claims in issued patents 5,362,755 (the parent of this case) and 5,547,994

(the grandparent of this case). As mentioned above, applicants believe that the references are merely cumulative to the references already of record.

The first reference, UK patent 1,298,494, discloses that R(-) albuterol is 50 times more potent than S(+) albuterol in antagonizing acetyl choline-induced bronchoconstriction in the guinea pig (page 1, column 2, line 68-74). The second new reference, German Patent 2,128,258, which corresponds to UK patent 1,298,494, but which has a slightly differently worded specification, refers to the "high pharmacological activity in particular of the R(-) isomers" and discloses without further quantification that R(-) albuterol "functions as an antagonist of the increased bronchial resistance which is caused in anesthetized guinea pigs as a consequence of acetyl choline."

Applicants' reference CB [Brittain *et al.* Brit. J. Pharmacol. 48, 144-147 (1973)], which was discussed extensively during prosecution of the '480 application and its parent 08/163,581, disclosed that mean equipotent doses for (-) and (+) albuterol in acetyl choline-induced bronchoconstriction in the guinea pig were 2.93 and 112 respectively. Thus applicants urge that the two new references add nothing to the existing record, and that the claims that were allowed in the '480 application and its parent, 08/163,581, remain allowable.

Since circumstances have compelled applicants to file this continuation, they have taken the opportunity to add a claim in the clearest possible format. The newly presented claim 23 combines the substance of the claims of the parent (now US patent

5,547,994), which relate to acute medication, with the substance of the claims of the grandparent (US patent 5,362,755), which relate to chronic medication, eliminating the division between acute and chronic, but making no other change. Since claim 23 is not of identical scope to any single claim of either issued patent alone, applicants believe it would not present an issue of statutory double patenting and would be allowable with a terminal disclaimer.

Respectfully submitted,

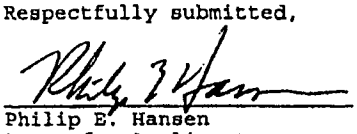

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EXHIBIT 18

GP1205

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Barberich *et al.* Docket No.: 0701.027D

Serial No.: 08/691,604 Group Art Unit: 1205

Filed: August 15, 1996 Examiner: Henley III, R.

#10/B
JRP
12/12/97

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Box Non Fee Amendment, Washington, D.C. 20231, on November 20, 1997.

Philip E. Hansen
Agent for Applicants
Reg. No. 32,700

Date of Signature: November 20, 1997

Assistant Commissioner for Patents
Box Non Fee Amendment
Washington, D.C. 20231

AMENDMENT AND RESPONSE UNDER 37 C.F.R. 1.111

Dear Sir:

This is a response to an Office Action mailed August 25, 1997 (paper number 9). As response to the Action is due by November 25, 1997, this paper is timely filed.

Amendment

Please amend the application as follows:

In the claims:

Please cancel claims 13 and 14.

Line 1 of claims 15, 16, 17 and 19, delete "13 or 14" and insert therefor --23--.

Response

The present application is a continuation of USSN 08/335,480, which included claims 1-12. All claims pending in the original application were canceled and new claims 13-23 were added in a preliminary amendment filed with the present application. Claims 13 and 14 are canceled herein; claims 15-23 are pending in this continuation application.

Statutory Double Patenting Rejection

Claim 13 was rejected as claiming the same invention as that of claim 1 of prior U.S. Patent No. 5,547,994 and claim 14 was rejected as claiming the same invention of claim 1 of prior U.S. Patent No. 5, 362,755. To overcome this rejection, both claim 13 and claim 14 have been canceled by amendment above.

Obvious-type Non-Statutory Double Patenting Rejection

Claims 13 and 15-22 were rejected as being unpatentable over claims 1-4 of prior U.S. Patent No. 5,547,994. Claims 14 and 15-22 were rejected as being unpatentable over claims 1-5 of prior U.S. Patent No. 5,362,755. Claim 23 was rejected as being unpatentable over claim 1 of prior U.S. Patent No. 5,547,994 and claim 1 of prior U.S. Patent No. 5,362,755.

In response to the above rejections, Applicants herewith submit Terminal Disclaimers in accordance with 37 CFR 1.321 (b) and (c) and fee under 37 C.F.R. 1.20(d).

Disclosure of Information under 37 CFR §1.56

In the prosecution of parent case 08/335,480 (now US patent 5,547,994), applicants presented a Declaration under 37 CFR §1.132 by John R. McCullough. Dr. McCullough presented results of tests on airway smooth muscle cells that demonstrated unexpected differences among the enantiomers and racemate of albuterol on calcium mobilization and on

airways hyperreactivity. Following the presentation of this declaration and the accompanying response on January 22, 1996, the claims were allowed. Earlier in prosecution, on June 6, 1995, applicants had presented a Declaration under 37 CFR §1.132 by Dean A. Handley showing the tremorogenicity of the enantiomers in mice. From the results in mice, Dr. Handley concluded that the use of the pure R enantiomer would result in less potential for tremorogenicity in humans. In the next Office Action following that declaration, the Examiner maintained the rejection and noted that the Handley declaration had been carefully considered, but it did not persuade the Examiner of error in his earlier rejection.

Subsequent to the prosecution of the '480 case, applicants have undertaken clinical trials in preparation for bringing the compositions and methods of the invention onto the market, including clinical trials directed toward determining tremorogenicity in humans. The results of the studies indicate that, notwithstanding the effects seen in the mouse tremorogenicity study, the S enantiomer does not appear to be tremorogenic in humans. Applicants therefore do not believe it would be proper to rely on the declaration of Dr. Handley for patentability. Applicants present this information in order to satisfy their duty of disclosure, but they believe it has no practical effect on the patentability *vel non* of the claims, since the Examiner did not rely on the declaration of Dr. Handley for his determination of allowability. As regards the findings in the declaration of Dr. McCullough, on which the Examiner appears to have relied for allowance, Dr. McCullough remains comfortable with the results and conclusions presented in that declaration.

There being no further outstanding issues, the application is believed in condition for allowance and such action is respectfully requested. However, should the Examiner have any further questions or comments regarding the pending claims, he is urged to contact Applicant's representative at the number below.

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
Reg. No. 32,700

Dated: November 20, 1997

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EXHIBIT 19

#3A
LB
6/12/98

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich *et al.* Atty Dkt. No.: 0701.027F

Serial No.: Unknown
Continuation of 08/691,604
Filed: August 15, 1996
Group Art Unit: 1205
Examiner: Henley III, R.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)ALBUTEROL

To: Assistant Commissioner for Patents
Box PATENT APPLICATION
Washington, D.C. 20231

Preliminary Amendment Under 37 C.F.R. 1.115

Dear Sir:

Prior to examination, please amend the application as follows:

In the Title:

Please delete "METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)ALBUTEROL" and substitute therefor --METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(-)ALBUTEROL--.

In the specification:

Page 1, between line 2 and line 3, insert:

--Cross Reference to Related Applications

This application is a continuation of ~~our prior copending~~ application 08/691,604, filed August 15, 1996, which ~~was~~ is now U.S. Patent 5,760,090,

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April 2, 1998

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continuation of application 08/335,480, filed November 7, 1994, now US patent 5,547,994, which was a continuation of application 08/163,581, filed December 7, 1993, now US patent 5,362,755, which was a continuation of application 07/896,725, filed June 9, 1992, now abandoned, which was a continuation of application 07/461,262, filed January 5, 1990, now abandoned.--

In the Claims:

Cancel claims 1-12.

Please add the following claims:

13. (New) A method of inducing bronchodilation or providing relief of bronchospasm, comprising administering to an individual a quantity of optically pure R-(-) albuterol sufficient to induce said bronchodilation.

14. (New) A method according to Claim 13, wherein the albuterol comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.

15. (New) A method according to Claim 13, wherein the albuterol comprises at least 99% by weight of the R(-) isomer and 1% or less by weight of the S(+) isomer.

16. (New) A method according to Claim 15, wherein the optically pure R(-) albuterol is administered by inhalation.

17. (New) A method according to Claim 16, wherein the optically pure R(-) albuterol is administered in an amount of about 30 μg to about 90 μg.

18. (New) A method according to Claim 15, wherein the optically pure R(-) albuterol is administered orally.

19. (New) A method according to Claim 18, wherein the optically pure R(-) albuterol is administered in an amount of about 1 mg to about 8 mg.

20. (New) A method according to Claim 18, wherein the optically pure R(-) albuterol is administered as a syrup.

21. (New) A method according to Claim 19, wherein the optically pure R(-) albuterol is administered as a syrup.

22. (New) A method of inducing bronchodilation or providing relief of bronchospasm while reducing the concomitant liability of adverse effects associated with racemic albuterol, comprising administering to an individual a quantity of optically

pure R-(-) albuterol sufficient to induce said bronchodilation while simultaneously reducing said adverse effects.

REMARKS

The present application is a continuation of US application, serial number 08/691,604. Claims 1-12 were present in the application as filed. All claims pending in the original application are canceled by amendment above and are replaced by new claims. Claims 13-22 are therefore pending in this continuation application.

In the parent application, 08/691,604, claims were allowed to "a method of treating asthma". New claims 13-22 relate to "a method for inducing bronchodilation or providing relief of bronchospasms". Support for the new wording relating to inducing bronchodilation or providing relief of bronchospasms is found on page 5, line 5-6, page 3, line 8-9 and elsewhere in the specification. Applicants respectfully submit that new claims 13-22 are allowable with a terminal disclaimer for reasons of record in parent application 08/691,604.

13

In order to expedite prosecution, Applicants enclose herewith terminal disclaimers in accordance with 37 CFR 1.321 (b) and (c) and fees under 37 C.F.R. 1.20(d).

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
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Dated: April 21, 1998

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A

EXHIBIT 20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al. Atty Dkt. No.: 0701.027H

Serial No.: Unknown
Continuation of 09/200,541
which was filed: November 25, 1998
Group Art Unit: 1614
Examiner: Henley III, R.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)ALBUTEROL

To: Assistant Commissioner for Patents
Box PATENT APPLICATION
Washington, D.C. 20231

Preliminary Amendment Under 37 C.F.R. 1.115

Dear Sir:

Prior to examination, please amend the application as follows:

In the Title:

Please delete "METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)ALBUTEROL" and substitute therefor --METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R(-)ALBUTEROL--.

In the specification:

Page 1, between line 2 and line 3, insert:

--Cross Reference to Related Applications

This application is a continuation of our prior copending application 09/200,541, filed November 25, 1998, which is a continuation of application 09/063,551, filed April 21, 1998, now US Patent 5,844,002, which was a continuation of application 08/691,604, filed August 15, 1996, now US Patent 5,760,090, which was a continuation of application 08/335,480, now US patent filed November 7, 1994,

5,547,994, which was a continuation of application 08/163,581, filed December 7, 1993, now US patent 5,362,755, which was a continuation of application 07/896,725, filed June 9, 1992, now abandoned, which was a continuation of application 07/461,262, filed January 5, 1990, now abandoned.--

In the Claims:

Cancel claims 1-12.

Please add the following claims:

13. (New) A method of treating bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(-) albuterol.

14. (New) A method according to Claim 13, wherein the albuterol comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.

15. (New) A method according to Claim 13, wherein the albuterol comprises at least 99% by weight of the R(-) isomer and 1% or less by weight of the S(+) isomer.

16. (New) A method according to Claim 13, wherein the optically pure R(-) albuterol is administered by inhalation.

17. (New) A method according to Claim 16, wherein the optically pure R(-) albuterol is administered in an amount of

about 30 μg to about 90 μg.

16. (New) A method according to Claim 15, wherein the optically pure R(-) albuterol is administered orally.

17. (New) A method according to Claim 16, wherein the optically pure R(-) albuterol is administered in an amount of about 1 mg to about 8 mg.

18. (New) A method according to Claim 16, wherein the optically pure R(-) albuterol is administered as a tablet, capsule or syrup.

19. (New) A method according to Claim 17, wherein the optically pure R(-) albuterol is administered as a syrup.

20. (New) A method of preventing bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(-) albuterol.

21. (New) A method according to Claim 20, wherein the albuterol comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.

22. (New) A method according to Claim 20, wherein the albuterol comprises at least 99% by weight of the R(-) isomer and 1% or less by weight of the S(+) isomer.

25. (New) A method according to Claim 22, wherein the optically pure R(-) albuterol is administered by inhalation.

26. (New) A method according to Claim 25, wherein the optically pure R(-) albuterol is administered in an amount of about 30 μg to about 90 μg.

27. (New) A method according to Claim 22, wherein the optically pure R(-) albuterol is administered orally.

28. (New) A method according to Claim 27, wherein the optically pure R(-) albuterol is administered in an amount of about 1 mg to about 8 mg.

29. (New) A method according to Claim 27, wherein the optically pure R(-) albuterol is administered as a tablet, capsule or syrup.

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REMARKS

The present application is a continuation of US application, serial number 09/200,541. Claims 1-12 were present in the original application 07/461,262, from which this application claims ultimate priority. All claims pending in the original application are canceled by amendment above and are replaced by new claims. Claims 13-29 are therefore pending in this continuation application.

In previous applications in this series, claims have been allowed to "a method of treating asthma" (08/691,604), to "a method for inducing bronchodilation or providing relief of bronchospasms" (09/063,551) and to "a method of treating an acute attack of asthma" (08/335,480). Applicants respectfully submit that new claims 13-29 to "a method of treating bronchospasm in a patient with reversible obstructive airway disease" and to a method of preventing bronchospasm in a patient with reversible obstructive airway disease" are allowable with a terminal disclaimer for reasons of record in parent applications 09/063,551 and 08/691,604.

In order to expedite prosecution, Applicants enclose herewith terminal disclaimers in accordance with 37 CFR 1.321 (b) and (c) and fees under 37 C.F.R. 1.20(d).

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
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Dated: December 17, 1999

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December 8, 1999

EXHIBIT 21

EXHIBIT REDACTED IN ITS ENTIRETY